Cortical Control of Smooth Pursuit Eye Movements

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Declaration

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Abbreviations

BA	Brodmann area
BOLD	Blood Oxygen Level Dependency
EEG	electroencephalography
EPI	echoplanar imaging
EOG	electrooculography
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
FWE	family wise error
IPL	inferior parietal lobule
LGN	lateral geniculate nucleus
MNI	Montreal Neurological Institute
MR	magnetic resonance
MT+	motion sensitive region
MT/MST	subregions of MT+
pCG	posterior cingulate gyrus
PCU	precuneus
PET	positron emission tomography
PPC	posterior parietal cortex
SC	superior colliculus
SEF	supplementary eye fields
SnPM	statistical non parametric mapping
SPEM	smooth pursuit eye movements
SPL	superior parietal lobule
SPM	statistical parametric mapping
V1	primary visual area

Abstract

In this PhD project, the functions of cortical regions that control smooth pursuit eye movements (SPEM) and visual attention were investigated. Combining behavioural (eye movement) measurements and functional magnetic resonance imaging (fMRI) the cortical areas participating in the processing of visual information and motor information were investigated. Overlapping cortical Blood Oxygen Level Dependency (BOLD) activations might indicate where the transformation of visual input information into a motor output response takes place. Furthermore, the influence of visual attention on these mechanisms was studied. In a third step, the location and function of subregions of the motion sensitive MT+ complex – which plays a crucial role in the control of SPEM – was explored in more detail. In the final experiment, functional differences between regions of the SPEM network during the processing of visual motion by varying the amount of coherently moving target dots were investigated.

In the first study it was shown that visual information processing takes place in the posterior parietal cortex (PPC) and MT+ and that oculomotor output processing takes place in the frontal eye fields (FEF), the supplementary eye fields (SEF), the cingulate gyrus and precuneus in addition to the above mentioned areas. Possible transformation sites were found in MT+ and within the PPC.

In the second study it was shown that processing of visual attention during SPEM is fully integrated in the SPEM network, but certain aspects of the control of attention like the dissociation of attention from gaze are especially processed in the PPC. Furthermore it was shown that the 'premotor theory' of Rizzolatti (1984) is also valid for SPEM.

In the third study two subregions of the motion sensitive MT+ complex, MST (medial superior temporal) and MT (middle temporal), were identified on group level. In contrast to monkey studies in the current study the eccentricity of the flow field relative to the midline played a minor role for the location of the MT+ subregions. These results question the assumed size of MT receptive fields in humans.

The fourth study revealed that the visual input signal is modulated by retinal information whereas the oculomotor output is modulated by the eye movement signal or a mixture of visual and oculomotor information. Integration of visual and oculomotor information seems to take place in MST and visual areas V7/LOP. Processing of differential motion of eye and background appears to take place in the PPC. Surprisingly PPC hardly reacted if eye and background moved in phase. Primary visual area V1 probably receives eye movement signals. Its functional connections and exact functional role need further investigation.

Zusammenfassung

In der vorliegenden Arbeit wurden die Funktionen von kortikalen Arealen untersucht, die glatte Augenfolgebewegungen (englisch: smooth pursuit eye movements, SPEM) und visuelle Aufmerksamkeit steuern. Durch kombinierte Messungen von Augenbewegungen (Verhaltensdaten) und funktioneller Magnetresonanztomographie (fMRI) wurden in der ersten Studie diejenigen kortikalen Areale untersucht, die an der Verarbeitung von visuellen und okulomotorischen Informationen beteiligt sind. Überlappende kortikale Blood Oxygen Level Dependency (BOLD)-Aktivierungen gaben Hinweise auf mögliche Orte der Transformation von visueller Eingangsinformation in eine motorische Ausgangsinformation. In der zweiten Studie wurde der Einfluss visueller Aufmerksamkeit auf diese Mechanismen geprüft. Im parieto-temporo-okzipitalen Kortex liegt eine Region, die visuelle Bewegung verarbeitet und daher auch bei der Steuerung von SPEM eine wichtige Rolle spielt, die Region MT+. In einer dritten Studie wurden detaillierte Untersuchungen zur Lokalisation und Funktion der Subregionen des MT+ Komplexes, durchgeführt. In einer vierten Studie wurden funktionelle Unterschiede zwischen Regionen des kortikalen SPEM-Netzwerks bei der Steuerung glatter Augenfolgebewegungen untersucht.

Die erste Studie zeigte, dass die Verarbeitung von visueller Eingangsinformation im posterioren parietalen Kortex (PPC) und in MT+ stattfindet und dass die Verarbeitung von okulomotorischer Ausgangsinformation, zusätzlich zu den beiden bereits genannten Regionen, in den frontalen Augenfeldern (FEF), den supplementären Augenfeldern (SEF), dem Gyrus cinguli und dem Präcuneus stattfindet. Mögliche Transformationsregionen wurden in MT+ und in einem Teil des PPC gefunden.

In der zweiten Studie wurde deutlich, dass die Steuerung von visueller Aufmerksamkeit während SPEM vollständig innerhalb des kortikalen SPEM-Netzwerks abläuft, allerdings finden bestimmte Aspekte der Aufmerksamkeitssteuerung, wie die Trennung der Aufmerksamkeit vom Blickpunkt, speziell im PPC statt. Zusätzlich wurde gezeigt, dass die „Prämotorische Theorie“ von Rizzolatti (1984) auch für SPEM Gültigkeit hat.

In der dritten Studie wurden zwei Subregionen des Bewegungs-sensitiven MT+ Komplexes, MST und MT, auf Gruppenebene identifiziert. Im Gegensatz zu Affen-Studien spielte in der hier beschriebenen Studie die Exzentrizität des Stimulusfeldes, in dem fließende Bewegung stattfand, von der Mittellinie eine untergeordnete Rolle für die Lokalisation der MT+-Subregionen. Dieses Ergebnis stellt die bisher allgemein angenommene Größe der rezeptiven Felder in der menschlichen MT-Subregion in Frage.

In der vierten Studie zeigte sich, dass das visuelle Eingangssignal retinal moduliert wird, wohingegen das motorische Ausgangssignal entweder durch Augenbewegungs-informationen oder durch eine Mischung aus retinalen und okulomotorischen Informationen moduliert wird. Die Integration von visueller und okulomotorischer Information scheint in MST und den visuellen Arealen V7/LOP stattzufinden, die Verarbeitung differentieller Bewegung von Auge und Hintergrund ist vermutlich im PPC lokalisiert. Erstaunlicherweise reagierte die Region PPC kaum, wenn sich Auge und Hintergrund gleichförmig (in Phase) bewegten. Das primäre visuelle Areal V1 scheint ebenfalls Augenbewegungssignale zu erhalten. Seine funktionellen Verbindungen und seine exakte funktionelle Rolle bedarf weiterer Erforschung.

Chapter 1

General Introduction

Motion rules the human world and moving objects are of vital importance for human beings. Moving objects can require an immediate motor response to avoid collisions while we participate in the daily traffic, if we want to catch an object like a ball or if we simply pour in a cup of coffee.

Usually, a moving object is observed carefully to gain information about its identity and relevance. For this purpose it must be brought onto the fovea, the location of the retina with the highest visual acuity, and be retained there. This is done with the help of selective visual attention (selects the object), saccades (fast eye movements which bring visual objects onto the fovea) and smooth pursuit eye movements (SPEM) (slow eye movements which closely follow the moving object thereby keeping it on the fovea).

SPEM, saccades and visual attention are controlled by widely distributed cortical networks which have been investigated in animal studies, in human patient studies and in functional imaging studies of healthy human subjects. However, to this day many of the functions of the different network regions and their co-operation remain unclear.

In this PhD project, the functions of cortical regions that control SPEM and visual attention were investigated. By combining behavioural (eye movement) measurements and functional magnetic resonance imaging (fMRI) it was aimed to reveal those cortical areas which participate in the transformation of visual input information into a motor output response. It was probed which areas process visual and which process motor information and where visual-to-oculomotor transformation takes place. Furthermore, the influence of visual attention on these mechanisms was studied. In a third step the motion sensitive middle temporal region MT+ which plays a crucial role in the control of SPEM was explored in more detail. It was studied how visual hemifield stimulation activated the MT+ complex in order to describe the role and function of its subregions. Finally, the SPEM-network was probed by varying the amount of coherently moving target dots (spatiotemporal frequency), in search for functional differences between network regions.

Smooth Pursuit Eye Movements

SPEM serve to keep the image of a moving object on the fovea, the area of the retina with the highest visual acuity and the highest concentration of colour sensitive receptor cells. The fovea only covers 1-2° of the whole visual field (overall about 180° of visual angle; Carpenter,

1988). Normally, SPEM need a visual object to be performed accurately (Rashbass, 1961). They are guided by the target velocity and the target position (Blohm et al., 2005; Pola and Wyatt, 1980). However, for short time periods SPEM can also be performed in anticipation or can be maintained when the target disappears (Barnes and Asselman, 1991; Bennett and Barnes, 2003; Joiner and Shelhamer, 2006; Kao and Morrow, 1994). Furthermore, they can be executed in complete darkness by some subjects, when they pursue an imagined target with their eyes e.g. their own finger (Gauthier and Hofferer, 1976). Mostly, we pursue objects that move across a structured, stationary environment (called background). Usually, retinal image motion of the visual background which moves across the retina during SPEM is neglected (Lindner et al., 2001), however the background information is most likely used to localise targets in space (Brenner et al., 2001; Leigh and Zee, 2006).

SPEM are rather slow continuous eye movements, mostly occurring at velocities slower than 40°/s (Leigh and Zee, 2006). The reaction time of SPEM is approximately 100-150 ms (Carl and Gellman, 1987; Kimmig et al., 2002). Their maximum speed is about 100°/s (Meyer et al., 1985). If SPEM cannot follow the moving target, so called catch-up saccades occur to bring the target back onto the fovea. At pursuit velocities of approximately 2°/s no saccades are needed. At higher velocities the amount of saccades increases up to the threshold for SPEM beyond which saccades are generated exclusively.

Before onset of smooth pursuit eye movements the image of the moving object moves across the retina. The initiation of SPEM is based on the resulting difference between position of the eye and position of the target (retinal error). The eyes start to drift. This initial pursuit directly reflects the processing of the neuronal motion detectors at a time when the eyes were not yet moving (so called open loop pursuit). Usually, this initial pursuit is not large enough to catch up with the target. Therefore a correction saccade is executed to bring the object onto the fovea. After this first correction saccade another 150-200 ms have elapsed such that feedback mechanisms can take control (so called closed loop pursuit) (Leigh and Zee, 2006). It is assumed that eye and target position are permanently compared and the difference between both (the retinal error) is minimized by adjusting the pursuit gain (Lisberger et al., 1987; Robinson et al., 1986; Yasui and Young, 1975). Closed loop pursuit is not only controlled by the feedback mechanism described above but also influenced by predictions about expected movements of the target.

Measures for the quality of pursuit of a sinusoidally moving target are gain (eye velocity/target velocity) and phase (temporal shift between target and eye motion) (Leigh and Zee, 2006). Perfect pursuit has a gain of 1 and no phase lag. For pursuit frequencies above 1 Hz (Pursuit frequency of a sinusoidally moving target of 1 Hz means that the duration of

one period of SPEM is 1s.), pursuit gain decreases rapidly, especially for higher amplitudes (15° and more). Parallel to this, the phase lag of the eyes relative to the pursuit target increases markedly (Leigh and Zee, 2006).

The control of SPEM is partially reflexive since they need a visual object to be executed, thus SPEM are often induced as a reflex to a moving object (Pola and Wyatt, 1991; Rashbass, 1961). Partially they are under voluntary control. Decisions must be made which object to pursue, furthermore SPEM can e.g. be induced voluntarily in darkness (Dukelow et al., 2001; Gauthier and Hofferer, 1976; Heywood, 1972); see above. In more recent studies it has been shown that SPEM share much of the cortical processing system which controls their execution with the one controlling saccadic eye movements (for a review of the two processing systems see Krauzlis et al. 2004).

Functional anatomy of SPEM

To this day the following cortical structures have been described to be involved in the control of smooth pursuit eye movements (Heide et al., 1996; Morrow and Sharpe, 1993; Morrow and Sharpe, 1995; Pierrot-Deseilligny, 1994). Input signals of a moving target traverse the lateral geniculate nucleus and arrive in the primary visual area V1. From there information is sent to the motion sensitive middle temporal visual region MT+ (human homologue of the monkey middle temporal and medial superior temporal area (MT/MST); (Maunsell and van Essen, 1983; Maunsell and Newsome, 1987)), the posterior parietal cortex (PPC) (Andersen et al., 1985; Maunsell and van Essen, 1983), the frontal eye fields (FEF) (Macavoy et al., 1991; Ungerleider and Desimone, 1986) and the supplementary eye fields (SEF) (Missal and Heinen, 2001; Tian and Lynch, 1996). Since patients with lesions in V1 can nevertheless perceive visual motion stimuli (this phenomenon is called blindsight), a parallel pathway from the retina to the MT+ complex, e.g. via the superior colliculus (SC) must exist (Stoerig and Cowey, 1997; Weiskrantz, 1996). Additional SPEM control areas are located in the cerebellum and in the brainstem but these are not the topic of this thesis and will not be considered here (For an overview see Fig. 1; for a detailed review see Krauzlis 2004 and Thier and Ilg 2005).

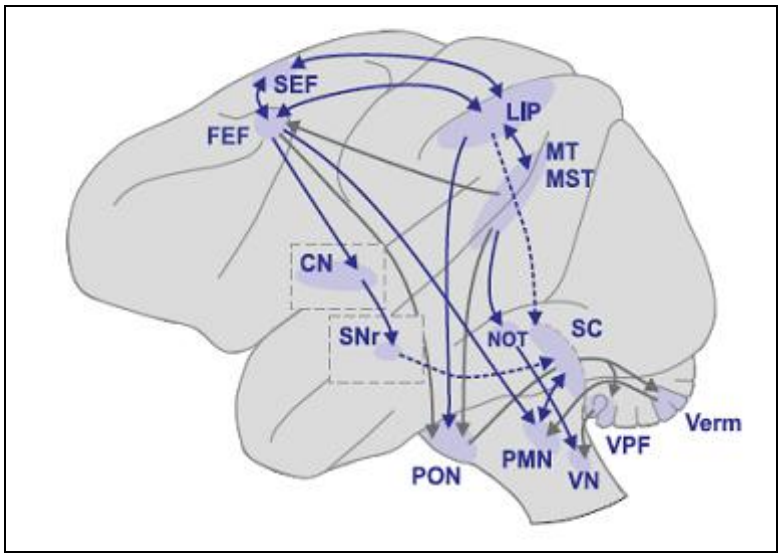

Fig. 1 adapted from Krauzlis 2004. Revised outline of the descending control pathways for pursuit eye movements. Schematic anatomical diagram of the descending pathways depicted on a lateral view of the monkey brain. Dashed arrows indicate presumed connections. Cortical areas (cerebellum and brainstem not included): SEF: supplementary eye fields; FEF: frontal eye fields; LIP: lateral intraparietal cortex; MT: middle temporal area; MST: medial superior temporal area; SC: superior colliculus; CN: caudate nucleus.

Visual attention

Nearly every visual scene contains various visual objects. However, our capacity to process different visual objects simultaneously is very limited (Eriksen and St James, 1986; Pashler, 1984; Pashler, 1994; Posner, 1980; Tong, 2004). By means of visual attention we can select relevant visual information and ignore irrelevant or distracting information.

Already in the 19th century William James (1890) distinguished passive, reflexive from active, voluntary attention. However, even now the term 'attention' is a matter of debate. A stimulus can attract attention reflexively/passively if it is distinctively different from its surrounding in shape, colour, orientation or movement or if it suddenly appears in our field of view (stimulus-driven attention control). Furthermore, attention can be actively focused on visual objects or parts of the visual field (goal-directed attention control) (Egeth and Yantis, 1997). So, via top-down attention mechanisms we can voluntarily control the processing of visual stimuli depending on their relevance for our actions (Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000).

Changes of location of attention (attention shifts) are usually accompanied by eye movements like saccades which present interesting objects on the fovea. We call them 'overt shifts of attention'. Yet it has been shown that attention shifts can also occur when they are not accompanied by eye movements. In this case they are called 'covert shifts of attention'

(Posner, 1980). It is common knowledge that processing of attended visual objects is easier than processing of non-attended objects (Luck et al., 1997; Posner et al., 1980). It is also known that attended stimuli can evoke stronger cortical Blood Oxygen Level Dependency (BOLD; for explanation see below) responses than non-attended stimuli (Culham et al., 1998; Tootell et al., 1998a) and that processing of distractors is suppressed (Desimone and Duncan, 1995). Furthermore, it is known that visual attention and saccades share most of their processing areas. (Buchel et al., 1998; Corbetta et al., 1998; Nobre et al., 2000) According to the "premotor" theory of attention (Rizzolatti et al., 1987), attention and eye movements are so closely linked that attention is oriented to a given point when the oculomotor program for moving the eyes to this point is ready to be executed.

However, to date visual attention research in relation with eye movements has nearly exclusively been limited to the saccadic system. Since SPEM and attention to moving targets might be of even greater importance in every day life (since moving targets are potentially dangerous), one of the goals of this thesis was to investigate where in the brain visual attention in relation to SPEM is processed.

In this thesis SPEM were investigated exclusively during fixation of the head. All studies were performed combining eye movement measurements and functional magnetic resonance imaging (fMRI). A short overview of these two methods follows below. For a detailed description of visual stimulation, subjects etc. see manuscripts.

MR Eye-tracking

Several methods can be used for measuring eye movements in humans: E.g. the electrooculography (EOG), video-based methods or the magnetic induction method (a contact lens with a small metal coil located on the eye which moves in the presence of a magnetic field). These methods have either limited spatial resolution (EOG), often they have limited temporal resolution (video) and/or involve magnetic material. However, to measure eye movements in the high magnetic field of a magnetic resonance (MR)-Scanner all metal and electronic devices near or inside the scanner must be avoided. Kimmig et al. (1999) presented a new limbus tracking device for high spatial and high temporal resolution eye movement recordings in the magnetic resonance (MR)-Scanner, which uses fibre optic technology (Kimmig et al., 1999). This Freiburg MR-eye-tracking system was used in all studies described in this thesis. The eye-tracker uses the fact that when the human eye is illuminated, more light is reflected from the white sclera than from the dark pupil and the iris. This differentially reflected light can be used to detect eye movements and calculate their

velocity and amplitude. Optic fibre cables (not magnetic!) are used to guide invisible infrared light (IR) from the eye-tracker into the MR-Scanner head coil and onto the eye of the subject. Two receiver cables are aligned to the nasal and the temporal limbus of the eye to transfer back the reflected IR light to two photo detectors. The difference signal between the inputs of the two photo detectors is amplified to a current with a range of ±5 V. The obtained high resolution current signal varies in correlation with the horizontal eye position; it can be analogue to digital converted and can be digitally stored.

Functional Magnetic Resonance Imaging (fMRI)

Since its introduction (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1990; Ogawa and Lee, 1990; Ogawa et al., 1992) fMRI has become a very widely used method for investigating the functions of the human brain. The advantage over other methods (e.g. Positron Emission Tomography (PET)) are its non-invasiveness, allowing repeated measurements and a higher spatial resolution e.g. compared to the electroencephalography (EEG) or magnetoencephalography (MEG) used in human research.

The fMRI method is based on the fact that hydrogen nuclei possess a spin. Hydrogen nuclei exist in the human body in specific concentrations in liquid (blood), brain tissue and fat. Their spins lead to specific magnetic characteristics of different brain tissues and also allow a measurable distinction between deoxygenated and oxygenated blood. Deoxygenated blood is paramagnetic, in comparison to oxygenated blood it has a different (high and positive) magnetic susceptibility which leads to a magnetic gradient near the blood vessels. This magnetic gradient causes a local decrease of signal (T2*-effect). This effect decreases when oxygenated blood, which is diamagnetic and has a very small and negative magnetic susceptibility, is transported to the local magnetic gradient. This leads to an increase of the signal (Belliveau et al., 1991; Hennig et al., 1995).

The so called Blood Oxygen Level Dependency (BOLD) signal – on which fMRI is based – utilizes this difference between oxygenated and deoxygenated blood and the typical physiological reactions of the brain. It has been shown to correlate with cortical local field potentials (Logothetis et al., 2001). When a cortical region is active after a small latency, the cortical blood flow (CBF) and the blood volume (CBV) are increased and more oxygenated blood is transported to the active region (Fox and Raichle, 1986; Logothetis et al., 2001). The time course of this signal is named the haemodynamic response function (HRF). This HRF is assumed to be heterogeneous across the cortices of individuals. In fMRI experiments the

HRF is determined by measuring the BOLD signal. This signal change of the measured BOLD signal is however very small (approx. 1-3%; Kwong et al., 1992).
Statistical brain data analysis tools like the brain data analysis software SPM (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/), which we utilized for our experiments, use a canonical HRF (BOLD function) as a model to correlate measured signal changes with the time course of a given stimulation or a task. The brain volume therefore is split into a large amount of voxels (little cubes of a resolution of e.g. 3x3x3mm^3, depending on imaging parameters). For each voxel of the brain, t-tests are performed to test if the actual voxel underwent significant BOLD changes which correlated with a given stimulus. If the data and the HRF model predicted from the time course of the stimulus correlate well in the given voxel, this location is assumed to be activated by the task.

Aims of the Thesis

The goal of this thesis was to investigate the functions of cortical areas participating in the control of SPEM and their modulation by visual attention.
The aim of the first project (SPEM-study) was to investigate which areas of the smooth pursuit system are involved in the processing of visual motion stimuli and which areas are related to the preparation of the oculomotor command. Special emphasis was laid on the question which cortical regions transform the visual (sensory) input information into a motor output command which moves the eyes. Note that visual information is represented in retinal coordinates while the motor information is given in head coordinates (and since the head is fixed, this is equivalent to space coordinates). That is, not only a visual to oculomotor transformation (sensorimotor transformation) must take place, but in addition a transformation of the coordinate frame is necessary (see manuscript 1: Sensorimotor and coordinate transformations in human cortex during SPEM).
Attention is able to modulate cortical activity. The aim of the second project of this thesis (Attention-study) was to investigate how covert shifts of attention during SPEM influence the activation of the cortical pursuit network and the oculomotor performance. The goal was to find out which brain regions control covert attention pursuit and if attention modulates the cortical pursuit network in general or if attention activates specific regions in addition to the SPEM system. Furthermore, it was studied whether the pursuit attention system is similar to the saccadic attention system found in other studies (see manuscript 2: Gaze pursuit, 'Attention pursuit' and their Effects on cortical activations).

In the third project (MT-subregions-study) the motion sensitive area MT+ of the smooth pursuit network was studied to find out more about the functions of the subregions of this area. It was aimed to reveal how ipsilateral motion stimuli close to the centre of the visual field activate the MT+ complex using low velocity flow field stimuli (see manuscript 3: Optic flow stimuli in and near the visual field centre: a group fMRI study of motion sensitive regions).

In the fourth and final project (Multiple-Dots-study) functional differences between network regions were investigated by varying the amount of coherently moving target dots (spatiotemporal frequency). In this way it was aimed to reveal properties of the retinal and extra retinal motion processing in the SPEM system (see manuscript 4: Modulation of BOLD activations of the SPEM network as a function of the amount of background dots).

Chapter 2

FMRI evidence for sensorimotor and coordinate transformations in human cortex during smooth pursuit eye movements

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Running head: Smooth pursuit recordings in fMRI

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Abstract

Smooth pursuit eye movements (SP) are driven by moving visual objects. The pursuit system processes the visual input signals and transforms this information into an appropriate motor output signal. Despite the object's movement on the retina and the eyes' movement in the head, we are able to locate the object in space implying coordinate transformations from retinal to head and space coordinates. To test for the visual and motor components of SP and the possible transformation sites, we used simultaneous precise eye movement measurements during fMRI, while presenting visual, oculomotor and visuo-oculomotor stimuli.

Visual components of activation during SP were located in the motion sensitive, parieto-occipito-parietal region MT+ and the posterior parietal cortex (PPC). Motor components comprised more widespread activation in these regions and additional activations in the frontal and supplementary eye fields (FEF, SEF), the cingulate gyrus and precuneus. The combined visuo-oculomotor stimulus revealed additional activation in the putamen. Possible transformation sites were found in MT+ and PPC. The MT+ activation evoked by the motion of a single visual dot was very localized, while the activation of the same single dot motion driving the eye was rather extended across MT+. The eye movement information appeared to be dispersed across the visual map of MT+. This could indicate a remapping of MT+, which is a precondition to encode the object trajectory in world-centered coordinates (rather than retinal coordinates) and to provide the basis for a motor output control. A similar interpretation holds for our results in the PPC region.

Introduction

In order to track a moving object, the pursuit system needs to analyze the velocity of the object. This requires visual information processing on the signal input side. Motion information has then to be transformed to a motor command signal, which is controlled by a feedback mechanism comparing eye and target motion (Krauzlis and Lisberger, 1994; Lisberger et al., 1987; Robinson et al., 1986; Young, 1971). Within the visuo-oculomotor transformation a coordinate transformation takes place (visual input coded in retinal coordinates, oculomotor output coded in head/space coordinates). If the eyes do not move, the retinal coordinate frame is equivalent to the head/space frame. Whenever the eyes do move, the resultant eye movement information needs to be integrated into the visual map.

The physiological circuits of the pursuit system are well known (Krauzlis, 2004; Thier and Ilg, 2005). Its anatomical correlates have been described in humans by lesion and imaging studies. Important cortical regions controlling SP are the striate cortex V1, the motion sensitive complex MT+ (corresponding to MT/MST in monkeys), the posterior parietal cortex PPC, the precuneus PCU, the frontal and supplementary eye fields (FEF, SEF) and the cingulate gyrus CG (Berman et al., 1999; Kimmig et al., 1999; Konen et al., 2005; Lencer et al., 2004; O'Driscoll et al., 2000; Petit and Haxby, 1999; Tanabe et al., 2002). Visual information is transferred from the retina via the lateral geniculate nucleus to V1, which contains neurons that respond to moving visual stimuli (Sincich and Horton, 2005). V1 projects to monkey MT/MST (Movshon and Newsome, 1996), which processes retinal as well as extraretinal (i.e. oculomotor) SP signals (Komatsu and Wurtz, 1988; Newsome et al., 1988). Dukelow et al. (2001) reported similar results in humans in an functional magnetic resonance imaging (fMRI) study by comparing visual and non-visual pursuit. However, non-visual pursuit is usually contaminated by saccades. Since these authors did not control for eye movements during scanning they might have measured saccadic activity as well. Saccade related activity indeed has been shown in the anterior part of MT+ in humans in the fMRI study by Petit and Haxby (1999). Further sites of possible visuo-oculomotor signal convergence are PPC, especially a putative human homologue to area VIP in monkeys (Bremmer et al., 2001), the posterior cingulate gyrus and the precuneus (Berman et al., 1999; Olson et al., 1996; Tanabe et al., 2002). FEF and SEF have been described to be involved generally in the planning and execution of oculomotor commands (Berman et al., 1999; Gagnon et al., 2006; Gottlieb et al., 1993; Heide et al., 1996; Heinen and Liu, 1997; MacAvoy et al., 1991; Missal and Heinen, 2004; Morrow and Sharpe, 1995; Petit and Haxby, 1999).

In this study we identified – by means of 3T whole brain fMR-imaging - the areas of the smooth pursuit system involved in the processing of visual motion stimuli and those areas related to the preparation of the oculomotor command. Special emphasis was placed on regions activated by visual as well as oculomotor and visuo-oculomotor conditions, because they represent possible sites of spatial coordinate transformation.

Materials and methods

Subjects

After giving their informed consent, 12 healthy volunteers participated in the study, which was approved by the local Ethics committee. The subjects' age ranged from 25 to 38 yrs (mean 28±5). All subjects were right-handed and had normal or corrected to normal vision.

MR-Eyetracker

For eye movement recordings we used the Freiburg MR-Eyetracker system, a fiber-optic limbus tracking device (Kimmig et al., 1999). A multi-channel computer program (LabVIEW®, National Instruments, Austin, Texas, USA) was used to acquire and display the signals derived from the MR-Eyetracker. The sampling frequency was 1000 Hz, the best spatial resolution was 0.2° of visual angle. The stimulus position was displayed and recorded in parallel to the eye movement data. The MR-scanner provided a TTL-pulse at the beginning of each volume acquisition. This pulse was used to trigger our stimulation and to provide an exact time marker for the eye movement acquisition programs. Calibration of eye position was performed prior and after each run. For calibration, subjects shifted their eyes repeatedly from the central fixation point towards targets at lateral locations of ± 5°.

MR-Imaging

Magnetic resonance imaging was performed with a 3 Tesla Magnetom TRIO research scanner (Siemens, Erlangen, Germany). The scanner was equipped with a send-receive circularly polarized headcoil (CP-Headcoil). Functional imaging was performed with T2*-weighted gradient recalled echo-planar imaging (EPI) sequences, equipped with a fully automated distortion correction (Zaitsev et al., 2004). High-resolution, sagittal T1-weighted images were acquired with the MP-RAGE (magnetization prepared rapid acquisition gradient echo) sequence to obtain a 3D anatomical scan of the head and brain. Shimming was performed for the entire brain using an auto-shim routine for magnetic field homogeneity.

The technical data for the functional measurements were TE = 30 ms, TR = 2.5 s, flip angle 90°, field of view 220 x 179 mm^2, matrix 128 x 104 and a voxel size of 1.7 x 1.7x3 mm^3. The stimulation protocol for each stimulation sequence consisted of twelve 25 s intervals with six alternating periods of rest (OFF) and stimulation (ON). This protocol produced 120 echo planar volumes per series. Data acquisition was performed in 28 slices per volume containing the whole brain except for ventral parts of the cerebellum. To minimize head motion, the subject's head was fixed in the MR headcoil. The effects of the gradient noises were reduced by sound-dampening headphones.

Visual Stimulation

Visual stimulation was created on a PC and back-projected onto a transluminent screen via an LCD-projector (NEC MT 1050, resolution 1024 x 758). Great care was taken to completely darken the room and to avoid stray light. The light of the projector was substantially reduced by two polarizing filters and by darkening the translucent screen such that, even after dark adaptation, subjects in the scanner saw nothing except the two visual stimulation dots. The screen was placed in the gantry at a distance of 65 cm to the subjects eyes (25° x 33° of visual angle).

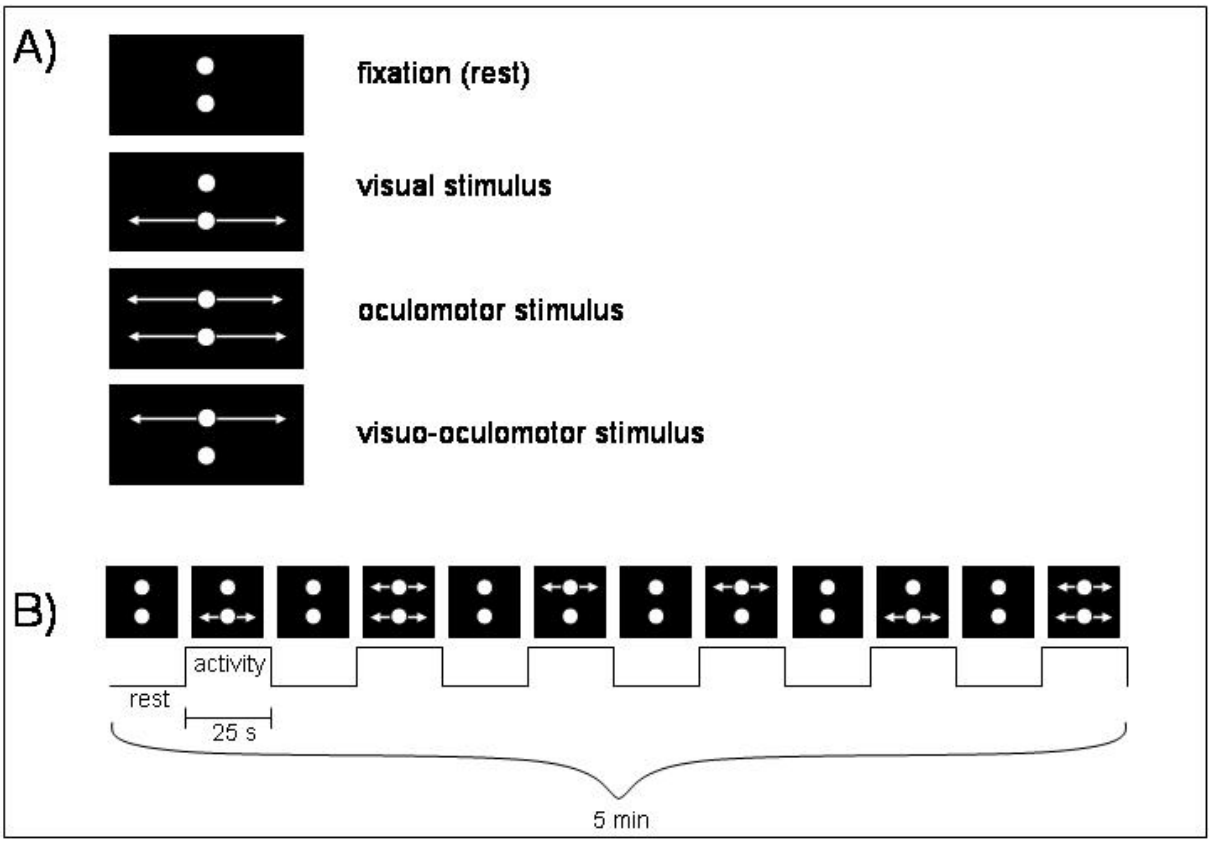

Fig. 1 Schematic drawing of stimuli. (A) Two vertically separated dots are presented in complete darkness. Both dots are either stationary (fixation/rest condition), or the lower dot moves sinusoidally in the horizontal plane (visual stimulation), or both dots move horizontally in parallel (oculomotor stimulation), or the upper dot moves horizontally, while the lower dot remains stationary (visuo-oculomotor stimulation). Task: Always fixate or pursue upper dot. (B) Sequence of rest and stimulation periods. After a rest period one of the three stimulation periods appeared in pseudo-randomized order. Each condition was presented twice within a series of 5 min duration.

A red dot (0.5° of visual angle) was projected 2° above the central screen position and a second red dot 4° below the position of the first dot. Both dots were continuously visible. During the rest period (duration 25 s) both dots remained stationary, subjects had to fixate the upper dot. Three different stimulation periods occurred (duration each 25 s): (condition 1) the lower dot moved sinusoidally in the horizontal plane and subjects had to fixate the stationary upper dot (resulting in pure visual stimulation due to the movement of the lower dot across the retina), (condition 2) both dots moved in parallel sinusoidally in the horizontal plane, subjects had to track the upper dot with their eyes (resulting in predominantly oculomotor and only little sensory/visual stimulation due to retinal slip – note, that with perfect pursuit there is no retinal slip; for ease of use we will call this the oculomotor stimulus - knowing that the result is in fact a visually driven oculomotor response), (condition 3) the upper dot moved sinusoidally in the horizontal plane and subjects had to track that dot with

their eyes, the lower dot remained stationary (resulting in visual stimulation due to relative motion of the lower dot across the retina plus additional visually driven pursuit motor activity with only minimal retinal slip stimulation; visuo-oculomotor stimulus; Fig. 1A). Either dot moved to ±5° at 0.16 Hz (peak velocity 5°/s). The three conditions (1. visual, 2. oculomotor, 3. visuo-oculomotor) occurred in a pseudo-random fashion. Each experimental condition was repeated twice and each condition was preceded by the rest period. Each subject performed three series (Fig. 1B).

fMRI data analysis

We used the software package SPM2 (Wellcome Department of Cognitive Neurology, London, UK) to analyze the T2*-weighted image series. Since residual head motion was evident in some of the image data despite head fixation in the scanner head coil, the first preprocessing step of the functional MRI data consisted in motion correction via SPM2 realignment. Then, for multiple-subject comparisons, we performed spatial normalization and smoothing with Gaussian spatial kernels of 6 mm (full width at half maximum). For statistical analysis data were fitted to a general linear model to establish parameter estimates for each subject. Contrasts were defined to yield the sizes of the main effects (1) visual stimulation (vs. fixation), (2) oculomotor stimulation (vs. fixation), (3) visuo-oculomotor stimulation (vs. fixation). Group level statistics was performed by including the individual contrast images for the three main effects into a random-effects within-subjects ANOVA. Please note, that the random-effects analysis takes into account both the within-subject variability as well as the between-subject variability. The specific effects were tested with appropriate T-contrasts. Clusters of 70 or more adjacent voxels surpassing an individual threshold of $p = 0.001$ (uncorrected) were considered as significant activations. This corresponds to a threshold $p = 0.05$ corrected for multiple comparisons on cluster level. Effect size was calculated for the maximally activated voxel in a given region of the visuo-oculomotor condition and compared to effect sizes in the same voxel of the visual and oculomotor conditions. Note, that the effect size is independent of the activation threshold (i.e. a given effect size may be well below the threshold and therefore not appear in the data of the glass brains, overlays or tables).

We report all findings in the MNI (Montreal Neurological Institute) coordinate system. Our study identified cerebral cortex and basal ganglia activations reflecting involvement of the smooth pursuit system. Cerebellar and brainstem regions were not included in the statistical analysis.

For visualization purposes we projected the functional group results onto the left and right hemispheres of the Human Colin surface-based atlas mapped to PALS ('Population-Average

Landmark- and Surface-based'-atlas; Van Essen, 2002; Van Essen, 2004; Van Essen, 2005). This atlas is derived from structural MRI volumes of 12 normal young adults. Data were mapped on the flatmap template and the three dimensional cortical template of the atlas. This was done using the Computerized Anatomical Reconstruction and Editing Toolkit (CARET) version 5.3 (Van Essen et al., 2001). Grid dimensions for conversion of analyzed volumes to CARET metric files were set to the SPM2 default values.

Statistical representations of the grey matter activations of the three main effects were mapped to different colours in functional overlays. Co-activated regions are displayed by weighted additive colour while pure colours indicate regions activated by only one of the tasks (visual – red; oculomotor – blue; visuo-oculomotor – green; intensity scale 0 – 255, the highest intensity referring to the maximum activation of each contrast).

Please note that only grey matter activations are visible in the flatmap presentation (clusters reaching into the adjacent white matter are truncated, which might explain slight differences as compared to the glass-brain activations). Furthermore, the flatmaps show only those activations and their overlaps surviving a T-threshold of 3.5 (i.e. flatmaps give no information about threshold independent effect sizes at a given location across tasks).

Eye movement data analysis

Previously we showed, how saccades influence the cortical BOLD activation (Kimmig et al., 2001). Therefore, eye movement data were analyzed separately for smooth pursuit eye movements and contaminating saccades using an interactive computer program. Saccade detection was performed by a velocity threshold algorithm (velocity threshold 50°/s). The algorithm detected saccades greater than 0.5°. Saccades smaller than 0.5° were determined interactively. Saccade detection below the noise level of 0.2° was not performed. We calculated the cumulative saccade amplitude per time interval and the number of saccades per fixation and stimulation period, respectively (saccadic frequency). Since saccades in the pursuit signal are to some degree inevitable, the measures of saccadic frequency and cumulative saccade amplitude indicate whether the measured saccades are balanced between rest and stimulation periods.

Pursuit eye position was filtered by a 3rd order polynomial filter (Sawatzky Golay) and differentiated to yield eye velocity. After extraction of saccades from the pursuit velocity trace, the remaining pursuit data were interpolated linearly. Artifacts like drifts or blinks were identified by visual inspection and removed. The eye velocity signal was then fitted by a Marquardt-Levenberg method (Borse, 1997) using three cycles of smooth pursuit. As a

measure for the goodness of SP performance we used the gain. Gain was defined by the ratio of eye velocity to target velocity (a gain of 1 represents optimal pursuit).

Results

Eye movement data

An example for eye movements obtained with the MR-Eyetracker during MR scanning is shown in Fig. 2A (upper trace).

Subjects almost perfectly tracked the target leading to a SP gain close to unity during both the visuo-oculomotor and the oculomotor task (Fig.2B; no statistically significant difference $p=0.3$). There was no measurable SP gain for the pure visual stimulation indicating that subjects fixated accurately. The occurrence of small corrective saccades increased slightly from the rest condition (fixation) to the visual stimulation and the pursuit conditions, however without reaching statistical significance (Repeated Measures ANOVA, $F(3, 11) = 1.3$, $p = 0.3$; paired t-tests, $p > 0.1$; Fig.2C). Similarly, cumulative saccade amplitudes were slightly larger in the pursuit conditions as compared to the fixation conditions, again without statistical significance (Repeated Measures ANOVA, $F(3, 11) = 0.9$, $p=0.4$). Since we calculated all our fMRI contrasts as activation contrasts versus the rest condition, we assume that saccade-related cortical activity plays a negligible role in all our contrasts.

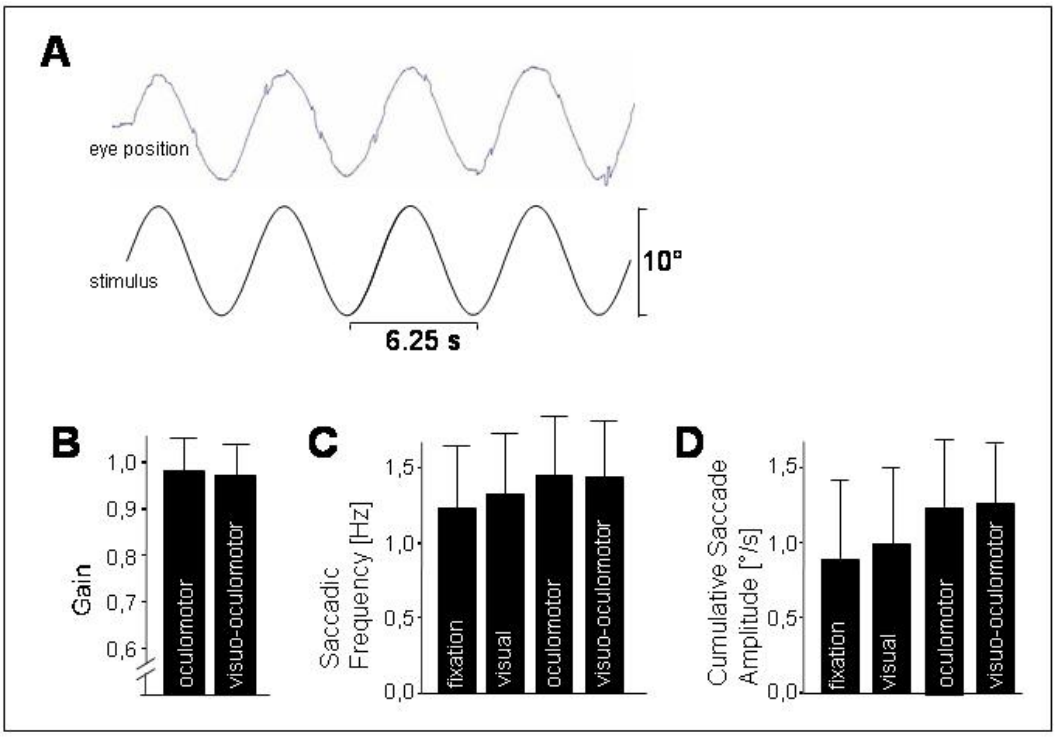

Fig. 2 (A) Example of original eye and stimulus position trace for one subject. (B) Smooth pursuit gain during oculomotor and visuo-oculomotor stimulation (mean±standard error). (C) Analysis of saccades occurring during the fixation and the three stimulation periods in terms of (C) number of saccades per second (saccadic frequency) and (D) cumulative saccade amplitude per second (mean±standard error).

fMRI data

Cortical activation (stimulation vs. rest) was found in V1, MT+, precuneus, posterior parietal cortex (PPC), SEF, FEF, the cingulate gyrus and parts of the basal ganglia. Visual stimulation activated mainly occipito-parietal regions MT+ and parts of the PPC (Fig.3A; for an overview on peak activations see table 1).

Oculomotor stimulation activated the frontal regions FEF and SEF, the cingulate gyrus, MT+, PPC, precuneus, cuneus and V1 (Fig. 3B).

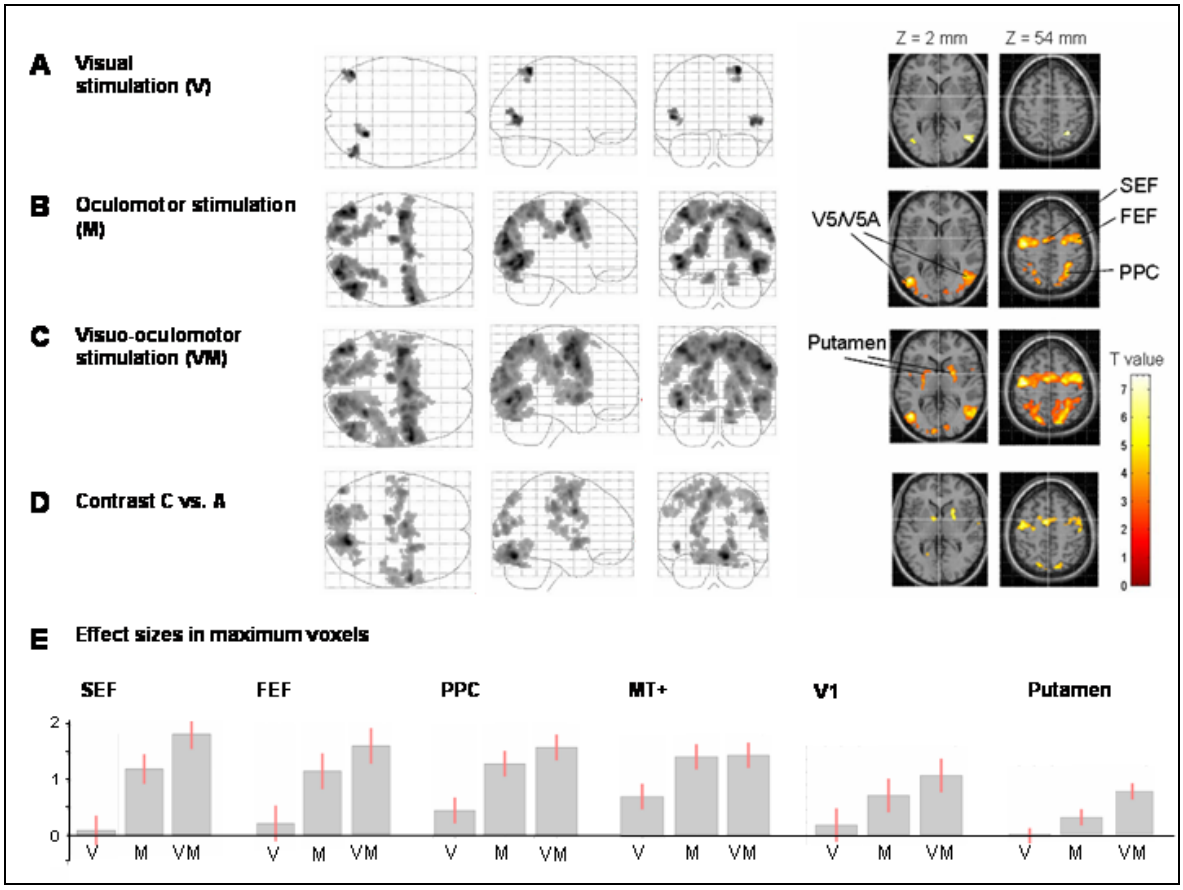

Fig. 3 Cortical activation related to (A) visual stimulation vs. rest, (B) oculomotor stimulation vs. rest, (C) visuo-oculomotor stimulation vs. rest, (D) contrast visuo-oculomotor vs. visual stimulation. Left hand panel, glass brains in three planes. Right hand panel, functional data overlaid on anatomical data, horizontal plane at two different z values. Random effects analysis, cluster level corrected, n=12. (E) Effect size in the maximally activated voxel of the visuo-oculomotor contrast (VM) in each of 6 different regions and corresponding effect sizes of the visual (V) and oculomotor (M) contrasts in the same voxel. Error bar is the standard error at this voxel.

The combined visuo-oculomotor stimulation yielded similar activations in the above mentioned regions, FEF and SEF, the cingulate gyrus, MT+, PPC, precuneus, cuneus and V1, but in addition also in parts of the basal ganglia, namely the putamen (Fig.3C).

In summary, pursuit related activity always involved the frontal regions FEF and SEF, while these regions remained almost silent during visual stimulation without eye movements.

Table 1. Activation locations of main contrasts

Anatomical Area	Visual Stimulation vs. Rest						Oculomotor Stimulation vs. Rest						Visuo-Oculomotor Stimulation vs. Rest					
	BA/fR	Voxel coord.			Cluster	T-Value	BA/fR	Voxel coord.			Cluster	T-Value	BA/fR	Voxel coord.			Cluster	T-Value
		X	Y	Z				X	Y	Z				X	Y	Z		
L Middle Frontal Gyrus							BA 6 (FEF)	-40	-6	62	1927	8.87						
R Medial Frontal Gyrus							SEF	2	-2	62	1927	7.78	SEF	8	-4	66	7740	9.63
L Medial Frontal Gyrus							SEF	-6	-4	56	1927	7.4	SEF	-6	-6	60	7740	11.18
R Precentral Gyrus													BA6 FEF	48	-4	52	7740	9.8
L Precentral Gyrus							BA 4(FEF)	-38	-12	54	1927	9.84	BA 6(FEF)	-41	-10	54	7740	11.19
R Superior Parietal lobule	BA 7	26	-54	66	183	5.91	BA7	28	-52	64	3747	6.74	BA 7	28	-52	62	6638	10.96
L Superior Parietal lobule							BA 7	-20	-66	62	811	6.37	BA 7	-16	-72	54	3925	8.17
R Inferior Parietal lobule								40	-34	40	3747	5.15						
L Inferior Parietal lobule							BA 40	-48	-36	38	173	5.64		-36	-48	-58	3925	6.33
R Precuneus	BA 7	28	-56	52	183	4.34	BA7	28	-58	54	3747	7.39		22	-76	36	6638	6.82
L Precuneus								-18	-66	40	811	4.81		-10	-78	48	3925	6.64
R Cuneus							BA 19	28	-88	20	3747	10.52		18	-78	46	6638	8.79
							V1	10	-84	16	3747	5.86	V1	12	-86	14	6638	7.06
L Cuneus							BA19	-18	-92	30	1697	7.02		-20	-88	30	3925	7.92
													V1	-8	-94	4	3925	5.8
L Lingual Gyrus													BA 18	-12	-88	-20	269	4.17
R Middle Temporal Gyrus								34	-80	18	3747	8.38		34	-80	18	6638	7.72
L Middle Temporal Gyrus							BA 37(V5)	-46	-68	4	1697	10.17	BA 37(V5)	-46	-68	4	3925	10.37
R Middle Occipital Gyrus	BA 37(V5)	54	-70	0	158	5.07	BA 19(V5)	46	-74	-12	3747	9.01						
L Middle Occipital Gyrus	BA 19(V5)	-48	-70	6	139	5.65	BA 19	-24	-86	18	1697	8.69						
							V1	-24	-88	12	1699	8.43						
L Inferior Occipital Gyrus													BA 18(V5)	-44	-80	-6	3925	12.23
R Inferior Temporal Gyrus	BA 37(V5)	44	-66	-2	158	5.17	BA 37(V5)	44	-66	-4	3747	10.45	BA 37(V5)	44	-66	-2	6638	10.04
R Putamen														22	2	-2	659	8.67
														20	12	2	659	6.4
L Putamen														-24	2	0	417	6.54
L Cingulate Gyrus								-12	-22	38	169	8.05		-12	-22	36	251	8.94
L Fusiform Gyrus							BA 19	-26	-84	-18	224	4.01						
L Lat Glob Pall														-24	-10	0	417	7.8

Voxel coordinates show the local maximum of an activated voxel cluster; BA = Brodmann Area; fR = functional region; T = T-value at voxel level.

Differential contrasts were calculated for visuo-oculomotor versus visual and visuo-oculomotor versus oculomotor conditions. The contrast between the visuo-oculomotor and the visual conditions revealed activation in FEF, SEF, cingulate gyrus, PPC, precuneus, cuneus and V1 as well as parts of the basal ganglia (Fig. 3D; table 2).

Table 2. Activation locations of differential contrasts

Anatomical Area	**Visuo-Oculomotor Stimulation vs. Visual Stimulation**					
	BA/fR	Voxel coord.			Cluster	T-Value
		X	Y	Z		
R Middle Frontal Gyrus	FEF	34	-2	54	724	4,28
L Middle Frontal Gyrus		-28	-10	64	528	5,17
R Medial Frontal Gyrus	BA6	50	0	44	724	5,97
	BA6 (SEF)	4	-2	62	744	5,99
L Medial Frontal Gyrus	BA6 (SEF)	-4	-4	58	744	7,53
R Precentral Gyrus	BA6 (FEF)	58	2	36	724	8,48
L Precentral Gyrus	BA6 (FEF)	-42	-8	56	528	6,24
R Postcentral Gyrus		58	-20	26	314	5,49
L Postcentra Gyrus		-46	-24	34	178	4,52
R Superior Parietal lobule		10	-80	52	240	5,23
L Superior Parietal lobule	BA7	-16	-72	54	157	5,72
R Inferior Parietal lobule		48	-32	50	72	3,97
R Precuneus		18	-76	46	240	4,39
L Precuneus		-14	-74	22	422	6,13
R Cuneus		24	-86	30	104	4,66
L Cuneus	BA17	-22	-82	10	422	6,33
L Middle Occipital Gyrus		-24	-84	18	422	6,32
L Inferior Occipital Gyrus	BA19 (MT+)	-44	-80	-6	98	7,3
L Lingual Gyrus	BA17/18	-12	-86	-18	2036	6
R Putamen		18	2	12	226	4,64
L Putamen		-14	6	6	80	3,67
L Cingulate Gyrus		-10	-22	40	205	6,59
L Med Glob Pall		-10	0	0	80	5,26
L Lat Glob Pall		-16	-2	-6	80	4,78
R Insula		46	-24	18	314	4,65
R Lentiform Nucleus		22	4	0	226	6,63
L Lentiform Nucleus		-16	-2	-6	80	4,78

Voxel coordinates show the local maximum of an activated voxel cluster; BA = Brodmann Area; fR = functional region; T = T-value at voxel level.

At the given threshold of T=3.5 (corrected for multiple comparisons on cluster level) more voxels were activated in the visuo-oculomotor condition as compared to the oculomotor condition. However, a direct comparison of the two contrasts did not reveal any significant difference (note, that also effect sizes of visuo-oculomotor and oculomotor activations in Fig. 3E were slightly, but not significantly different). The reversed contrasts also did not show any significant voxels.

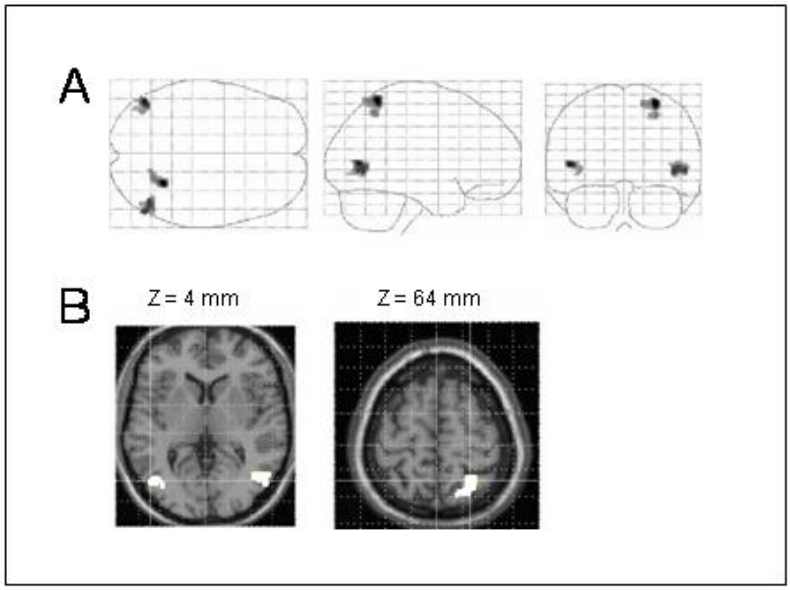

Fig 4 Conjunction analysis indicating regions activated by all three stimuli. (A) Glass brains in three planes. (B) Functional data overlaid on anatomical data, horizontal plane at two different z values. Random effects analysis was applied.

A conjunction analysis (Price and Friston, 1997) revealed significant activations ($n = 12$; $p < 0.05$, cluster level corrected) common to all three conditions in regions MT+ and PPC (putative sensorimotor transformation sites; Fig.4).

The local distribution of task-dependent activations was visualized by calculating flat maps with overlays of all three contrast types (visual – red, oculomotor – blue, visuo-oculomotor – green). Within a given region we could identify subregions, which were correlated to the one or the other stimulation type (Fig. 5). Furthermore, we could visualize sites of overlapping activations (putative transformation sites) depicted as whitish regions (color mix of red-blue-green; remember that these flatmaps exclusively represent gray matter activations above a threshold of T=3.5; white matter activations, cerebellar activations and statistical significances across tasks cannot be seen in this visualization).

In general, the visual stimulus evoked much less cortical activation as compared to the oculomotor or the visuo-oculomotor stimulus. A large overlap of activation of all three stimuli

occurred in the MT+ regions of both hemispheres, a further activation overlap was located in the right posterior parietal cortex. For the oculomotor and visuo-oculomotor stimuli, additional bilateral activation overlaps were located in the FEF, SEF, cingulate gyrus, precuneus, cuneus including V1and in the PPC.

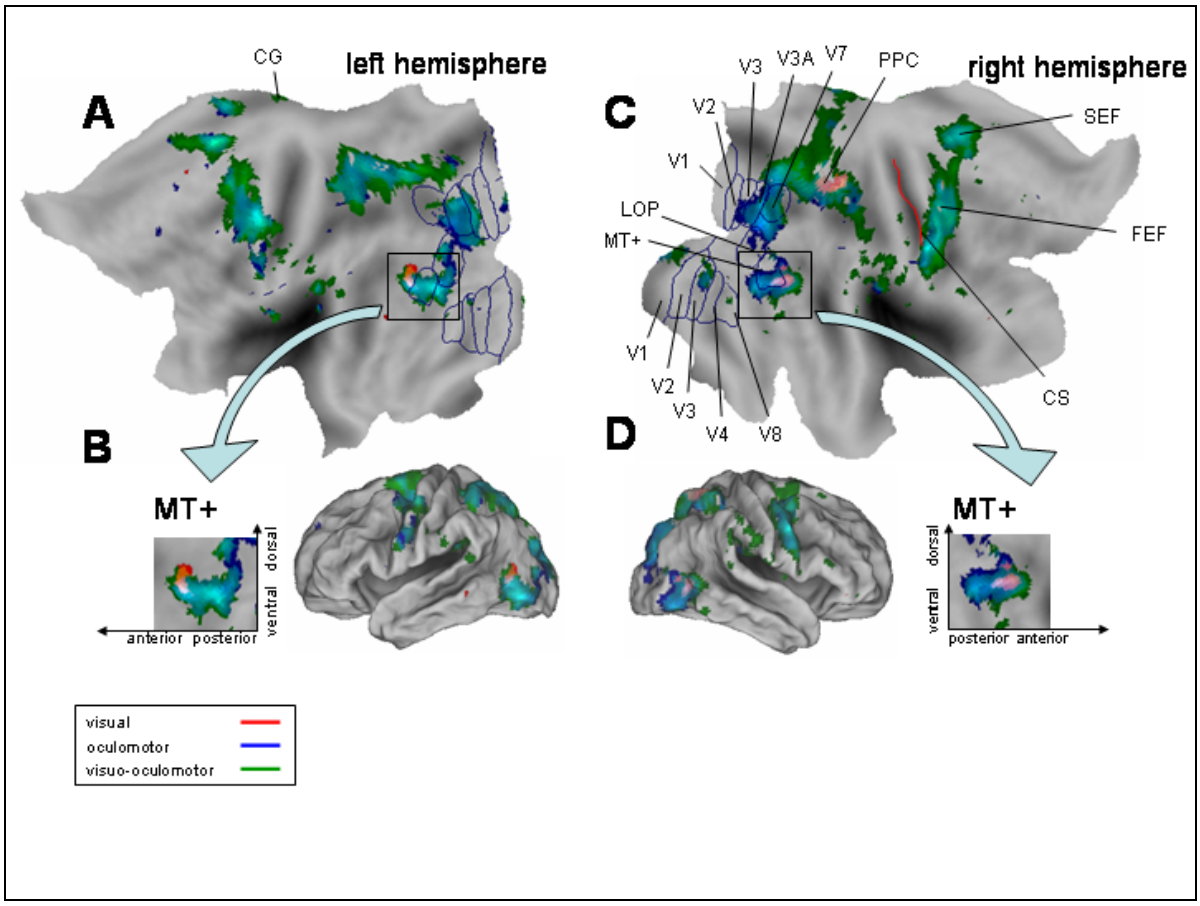

Fig. 5 Flatmaps of the (A) left and (C) right hemisphere. Functional data overlaid on flattened template brain. Functional data are RGB colour-coded, intensity scaled to arbitrary values between 0-255; Red, visual stimulation; Green, visuo-oculomotor stimulation; Blue, oculomotor stimulation; threshold, T=3.5. To ease interpretation of the flatmaps, a map of visuotopic areas is overlaid (outlined in black, taken from (Van Essen, 2005); furthermore, insets below show a lateral view on the just slightly inflated 3D PALS template brain with overlaid activations. Enlarged flatmap versions of left region MT+ (Fig. 5B), and right region MT+ (Fig. 5D). CG - cingulate gyrus. CS - central sulcus. LOP – lateral occipital parietal.

Multimodal regions

MT+: All three stimuli led to partially overlapping activations in area MT+ (Fig. 5A, C, with conditions for visual (red), oculomotor (blue), and visuo-oculomotor (green) stimulation). Within this region, the visual activation was located in the anterior, dorsal part, in both hemispheres (Fig. 5B, D). Visuo-oculomotor and oculomotor activations were more distributed and largely extended in the posterior and ventral part of this region.

PPC: A further overlapping region activated by all three stimuli was evident in the right posterior parietal cortex. The region activated by the visual condition is rather circumscribed whereas the visuo-oculomotor and the oculomotor conditions evoked much more extended activations. No other overlapping regions activated by all three stimuli could be found on the flat maps of the whole cortex.

Discussion

To our knowledge, this is the first study to compare the cortical activation resulting from the motion of a single dot across the retina with the activation resulting from ocular pursuit. We were able to identify the cortical regions processing visual stimuli, the regions processing oculomotor stimuli and the regions being involved in visuo-to-oculomotor transformation.
Pursuit performance in our experiments was almost perfect, small correction saccades (amplitude < 1.2°) occurred similarly during both the rest and stimulation periods. Since we calculated all our main contrasts against the rest condition residual BOLD responses should have cancelled out in all the contrasts. In line with our previous study, one would expect no effect for saccade amplitudes between 2-10°, and possibly no effect for the small amplitudes of about 1° (Kimmig et al., 2001).

Sensory Input
During fixation, a single visual motion stimulus (visual condition) activated parts of the motion-sensitive complex MT+ and the PPC. These regions are obviously involved in visual motion processing. In contrast, we could not see any activation in primary visual areas surviving the threshold. It appears that the relative motion of two visual dots in darkness (as compared to two stationary dots) did not induce measurable additional activation in striate cortex. Furthermore, SEF and FEF do not appear to be involved in sensory processing of the visual motion (and the potential pursuit) stimulus during the fixation task.

Oculomotor Output
Ocular pursuit of a small moving target with a second target moving in phase (oculomotor condition) induced more widespread activation in PPC, and MT+ and additional activation in precuneus, cuneus and V1, the cingulate gyrus, SEF and FEF. Thus, in addition to the parieto-occipital regions involved in sensory input processing, the oculomotor task caused activation in more frontal regions. This implies that SEF and FEF are involved in processing and control of oculomotor output signals (Heide et al., 1996). The activations we found in

precuneus and the cingulate gyrus have been described previously during pursuit. The posterior cingulate is thought to play a role in integrating sensory and motor signals to guide ongoing eye movements (Berman et al. 1999, Olson et al. 1996).

The combined visuo-oculomotor stimulus (ocular pursuit of a small moving target with a second target remaining stationary) activated regions similar to those active in the oculomotor stimulus, with additional activation in the putamen. Generally, the amount of voxels being activated above the threshold of T=3.5 tended to be higher in the visuo-oculomotor condition as compared to the oculomotor condition. However, the direct comparison of the two contrasts did not show statistically significant differences in any pursuit related region. Similarly, the maximum effect sizes across these two conditions differed slightly without reaching the significance level.

The involvement of basal ganglia structures in human smooth pursuit eye movements is a novel finding. In monkey, the basal ganglia have been shown to be involved in ocular pursuit only recently (Basso et al., 2005; Cui et al., 2003). Furthermore, putamen neurons were strongly active when movements were withheld or self-timed (Lee et al., 2006).

In V1, we obtained no activation in the visual task, but comparable small activations in the oculomotor and visuo-oculomotor tasks. Thus, pursuit eye movements appeared to slightly activate V1. Since the experiment was performed in complete darkness (even after dark adaptation, subjects could see nothing else but the two dots), no other visual stimuli (like scattered light) could explain this result. Retinal slip during pursuit might have added to the V1 response. Remind however, that pursuit gain was close to optimal. Furthermore, an extraretinal source of the V1 activation could be assumed. Indeed, in a saccade task, V1 activation has been found to be related to spatial updating, or remapping (with remapping as one neural mechanism by which the brain compensates for shifts in the retinal image caused by voluntary eye movements; Merriam et al., 2007).

Sensorimotor Transformation

The regions activated by all three conditions, as shown by the conjunction analysis (Fig. 4), are MT+ and PPC. These two regions appear to be involved in both sensory and oculomotor processing and represent possible sites of sensorimotor transformation.

MT+. In the flat map presentation, our visual stimulus (motion of a single dot) activated a rather circumscribed subregion of MT+ in the dorsal anterior part. This has not been shown so far, because traditionally large field or multi-dot motion patterns were used to stimulate MT+ in previous studies (e.g. Dukelow et al., 2001; Huk et al., 2002; Tootell et al., 1995b). In contrast, ocular tracking of a single moving dot (oculomotor as well as visuo-oculomotor

stimulus) yielded strong and widespread activation, extending into ventral and posterior parts. This is a remarkable result considering that the physical stimulations in the visual and the visuo-oculomotor conditions were comparable (two dots, one moving, one stationary). In other words, while the processing of a single visual dot's motion was very localized, the processing of the same single dot motion driving the eye was rather extended across the MT+ region. We assume that the eye movement information is dispersed across the visual map of the MT+ region. This could be indicative of a remapping of MT+. The new MT+ map would then encode the object trajectory in world coordinates (i.e. transform the retinal to a head/space coordinate system).

Indeed, it has been shown that, in monkey, MT and MST neurons also code for eye position and are capable of representing motion in world-centered coordinates (Bremmer et al., 1997; Ilg et al., 2004). Similarly, a recent imaging study showed that the response of human V5 is modulated by gaze direction (d'Avossa et al., 2006).

Since the visually driven pursuit stimuli possibly activate most of the motion sensitive region MT+, a further division in sensory and motor subregions V5 and V5A is not possible in this experimental setup.

It is well known that region MT+ corresponds to the junction of Brodmann areas 19, 37, 39 in humans and MT/MST in monkeys. Area MT in monkey processes visual motion stimuli, while area MST, adjacent to MT in the anterior direction, in addition gets non retinal input about on-going eye movements (Komatsu and Wurtz, 1988; Newsome et al., 1988). Therefore, the MT+ complex receives visual and motor inputs (motion on the retina, eye motion in the head), which enable this area to process motion relative to the head, i.e. to perform a coordinate transformation. In humans, the motion sensitive region MT+ was identified in early studies (Tootell et al., 1995a; Tootell et al., 1995b; Tootell and Taylor, 1995c; Zeki et al., 1991). Evidence for a spatial separation in V5 and V5A (in analogy to MT and MST in monkey) has been sparse as of date. Huk et al. (2002) found some evidence by testing the different visual properties of these two subregions in 5 subjects, however with considerable inter-subject variability. Dukelow et al. (2001) described a subregion that was activated by non-visual pursuit, i.e. putative V5A, being located in the anterolateral portion of the MT+ complex in 5 subjects. Non-visual pursuit is however difficult to perform and was uncontrolled in their task (i.e., no in-scanner eye-tracking). Although not explicitly stated, their data suggest that visual pursuit led to extended activation of MT+, comparable to the activation evoked by wide field optic flow during fixation. The work of Dukelow et al. (2001) therefore indirectly supports our assumption that pursuit of a single dot in darkness activates most of the region MT+.

PPC. A further region processing the visual and oculomotor signals in our study is located in PPC. Similarly to the MT+ region, motion of a single dot led to a localized PPC activation, while the same single dot motion driving the eyes led to widespread PPC activations. Remapping could be an explanation in the PPC region, too. In the monkey, neurons in area 7a of the parietal cortex code for eye position in space rather than position of a target on the retina (Andersen et al., 1990). In further studies, the intraparietal sulcus has been shown to be an area of convergence of multimodal stimuli (Andersen et al., 1997). Several subregions have been identified, each subserving specific functions (Grefkes and Fink, 2005). Of special interest for the functions investigated in this study is area VIP (ventral intraparietal). VIP receives input from motion, oculomotor, vestibular, tactile and auditory stimuli (Bremmer, 2005). The overlapping region seen in our experiments in PPC responds in visual motion and pursuit tasks and is most likely the human homologue to area VIP in monkey, in accordance with a previous study (Bremmer et al., 2001).

Superordinate functions (attentional processes)

In addition to visuo-oculomotor transformation, other functions may be related to the activation in MT+ and PPC as well, like attention mechanisms. Attentional processes are important for both visual and oculomotor motion processing and therefore lead to stimulus independent activation, representing a kind of superordinate function. Indeed, attentional load has been shown to modulate cortical activation during pursuit. Attention specific activation was however only observed in the PPC (Kimmig et al., 2006).

Conclusion

Our results show that the sensory input processing during smooth pursuit eye movements is performed in parieto-occipital regions MT+ and PPC, while oculomotor output processing involves the frontal regions FEF, SEF, the cingulate gyrus and precuneus. The V1 activation during SP is possibly of extraretinal origin. The source of this rather weak signal remains open and needs further investigation. Furthermore, parts of the basal ganglia play a role in ocular pursuit. Sites for visuo-motor transformation or retinal to head/space coordinate transformation are MT+ and PPC (most likely the homologue to monkey VIP). We suggest that during the transformation process the eye movement signal is continuously dispersed across the visual map. This updated visual map at the MT+ level can be used to guide the motor output in head/space coordinates. While MT+ is involved in the integration of visual and oculomotor motion signals, the second transformation region we found, PPC, is capable of integrating polymodal signals (visual, motor, somatosensory, acoustic, effects of attention

etc.). Further investigations of task sharing and interaction between these two regions are needed for a thorough description of their functional specialization during smooth pursuit eye movements.

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Chapter 3

Gaze pursuit, 'Attention pursuit' and their Effects on cortical activations

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Running head: Gaze and Attention pursuit in fMRI

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Abstract

A moving object draws our attention to it and we can track the object with smooth pursuit eye movements (SPEM). Gaze and attention are usually directed to the same object during SPEM. In this study we investigated whether gaze and attention can be divided during pursuit. We explored the cortical control of ocular tracking, attentive tracking and the role of focused and divided attention. We presented a sinusoidally moving target for pursuit and simultaneously a stationary target for fixation. Gaze could be directed to the pursuit target and attention to the fixation target or vice versa, or gaze and attention were directed to the same – moving or stationary - target. We found that gaze (overt) and attentive (covert) pursuit similarly activated the cortical oculomotor network. Gaze pursuit showed higher activations than attentive pursuit. Activations, specific to the dissociation of attention from gaze and independent of eye movements, were found solely in the posterior parietal cortex (PPC). A cue indicating a forthcoming attention task activated large parts of the cortical SPEM network, as a kind of preparatory mechanism. We did not find any attention-related regions outside the well-known visuo-oculomotor network. We conclude that attention control during gaze pursuit and gaze fixation occurs within the cortical SPEM network, supporting the premotor theory of attention (Rizzolatti et al., 1987).

Keywords

Eye movements - fMRI – human - parietal cortex - premotor theory

Introduction

The fovea is the location on the retina with the highest visual acuity. Objects of interest are projected to the fovea with the help of eye movements. Relevant moving objects like a prey, a potential predator or a fast moving vehicle should be scrutinized which is facilitated by smooth pursuit eye movements. Before execution of visual pursuit the SPEM system needs to first detect the moving object, visual attention should then be focused on it, its velocity needs to be processed and a motor signal to the extraocular muscles has to be prepared to allow pursuit. Although it has been argued (Kathmann *et al.*, 1999) that SPEM were executed automatically and thus do not depend on attention, others confirmed the importance of attention for accurate pursuit performance (Wyatt & Pola, 1987; Hutton & Tegally, 2005). Furthermore, it has been shown that during SPEM visual attention is located close to the focus of gaze (Van Donkelaar & Drew, 2002).

During steady gaze fixation it has been shown that the focus of attention can be separated from the focus of gaze (Posner, 1980). The effects of such visual attention shifts were investigated using positron emission tomography (PET; Corbetta *et al.*, 1993), PET & functional magnetic resonance imaging (fMRI; Coull & Nobre, 1998) and fMRI (O'Craven *et al.*, 1997; Buchel *et al.*, 1998; Corbetta *et al.*, 1998; Culham *et al.*, 1998; Gitelman *et al.*, 1999; Wojciulik & Kanwisher, 1999; Corbetta *et al.*, 2000; Hopfinger *et al.*, 2000; Nobre *et al.*, 2000; Perry & Zeki, 2000; Culham *et al.*, 2001; Jovicich *et al.*, 2001; Yantis *et al.*, 2002; Astafiev *et al.*, 2003). For investigation of attentional processes during fast, goal-directed eye movements to a peripheral target (saccades), several of these studies compared effects of attention shifts without saccades (so-called covert shifts of attention; with gaze fixation) to attention shifts in parallel with saccades (overt shifts of attention; equivalent of normal saccades) [1-7]. Bilateral activations during covert shifts of attention and during saccades were located in parts of the premotor cortex (frontal eye fields, FEF; supplementary eye fields, SEF), parts of the parietal cortex (involving intraparietal sulcus and /or superior parietal lobule, SPL) (Beauchamp *et al.*, 2001; Astafiev *et al.*, 2003) and, in addition, in parts of the posterior temporal cortex (the motion sensitive region MT+, corresponding to MT/MST in monkey; Corbetta *et al.*, 1998; Nobre *et al.*, 2000). Thus, as a common result, the cortical network for directing the focus of visual attention seemed to overlap widely with the network for saccadic eye movements. This finding supports the premotor theory of attention, which postulates a strict link between covert orienting of attention and programming explicit ocular movements: attention is oriented to a given point when the oculomotor program for moving the eyes to this point is ready to be executed (Rizzolatti *et al.*, 1987). The above mentioned

findings led to the conclusion that covert attention shifts and saccades are subserved by similar neural mechanisms.

The human cortical pursuit network has been studied by fMRI (Berman *et al.*, 1999; Kimmig *et al.*, 1999; Petit & Haxby, 1999; Schmid *et al.*, 2001; Rosano *et al.*, 2002; Tanabe *et al.*, 2002). However, to our knowledge there is only one fMRI study, which investigated covert attentive tracking, but not during pursuit eye movements (Culham *et al.*, 1998). An investigation of continuous, covert attentive tracking ('attention pursuit') in relation with smooth pursuit eye movements (gaze pursuit) is lacking so far. Thus, the role of attention during overt and covert pursuit remains a matter of debate, although this issue is of major importance in everyday life: it happens constantly that we pursue something with our eyes but at the same time we must be able to attend to the motion of something else (e.g. pursuing a ball and attending to a neighboring player; pursuing an approaching car and attending to an approaching vehicle from another direction).

We examined covert shifts of attention during ongoing smooth pursuit eye movements. We investigated cortical activations (i) during pursuit of a moving target or (ii) fixation of a stationary target. In either condition, attention and gaze directions could be focused on the same target location (termed: focused attention condition) or attention direction could be divided from gaze direction by shifting attention to a second target (termed: divided attention condition). The second target could also be moving or stationary. Thus, we were able to investigate overt gaze pursuit, covert attention pursuit and the effects of focused and divided attention.

We asked how covert shifts of attention during SPEM influence the activation of the cortical pursuit network and the oculomotor performance. Which brain regions control covert attention pursuit? Does attention modulate the cortical pursuit network in general or does attention activate specific regions in addition to the SPEM system? Is the pursuit attention system similar to the saccadic attention system found in other studies?

Material and Methods

Visual Stimulation:

Visual stimulation was generated by a computer and back-projected via video beamer (PLUS Vision, Tokyo, Japan, resolution 1024x768 pixels) onto a translucent screen at the back of the scanner gantry. The light of the beamer was reduced by polarizing filters and by darkening the translucent screen such that subjects in the scanner saw nothing except the two visual stimulation dots. Thereby we excluded unwanted motion stimuli on the retina resulting from eye movements. Subjects viewed the stimuli via a mirror mounted on the scanner headcoil.

The visual stimulus consisted of two red circular dots (0.5° of vis. angle, 4° vertical distance). Visual stimulation was performed in a block-design. Each trial consisted of a cue period (12.5 s), a stimulation period (25 s) and a rest period (10 s; Fig. 1).

During the cue period, the two stationary, circular dots changed to somewhat larger squares in fifty percent of the trials. This cue indicated to the subject to shift attention to the lower dot during the subsequent stimulation period. After 4 seconds the squares switched back to circular dots for a duration of 8.5 s, which served as washout period for any cue-related Blood Oxygen Level Dependency (BOLD) changes. Hereby we avoided a contamination of cue-related BOLD activations with subsequent stimulation-related activations.

During stimulation, either the upper or the lower dot moved sinusoidally in the horizontal direction (amplitude ±5° at 0.16 Hz, peak velocity 5°/s). Four different stimulus conditions were tested: (A) gaze and attention directed to the moving upper dot, the lower dot being stationary (‘gaze pursuit attention pursuit’; Fig. 1A), (B) gaze pursuit of the moving upper dot, but attention directed to the stationary lower dot (‘gaze pursuit attention fixation’; Fig. 1B), (C) attention and gaze directions located on the stationary upper dot with the lower dot moving (‘gaze fixation attention fixation’; Fig. 1C), (D) gaze located on the upper dot, but attention directed to the moving lower dot (‘gaze fixation attention pursuit’; Fig. 1D). The labelling A-D for the four stimulus conditions will be kept throughout the text and figures.

During the rest condition the two dots remained stationary.

Please note, that in stimulus conditions (A) ‘gaze pursuit attention pursuit’ and (C) ‘gaze fixation - attention fixation’ the directions of attention and gaze were focused on the upper dot (focused attention conditions), while in conditions (B) ‘gaze pursuit attention fixation’ and (D) ‘gaze fixation attention pursuit’ the directions of attention and gaze were divided (divided attention conditions; attention on lower dot, gaze on upper dot). Furthermore, condition (A)

'gaze pursuit attention pursuit' denotes an overt pursuit task. The condition (D) 'gaze fixation attention pursuit' refers to a covert pursuit task.

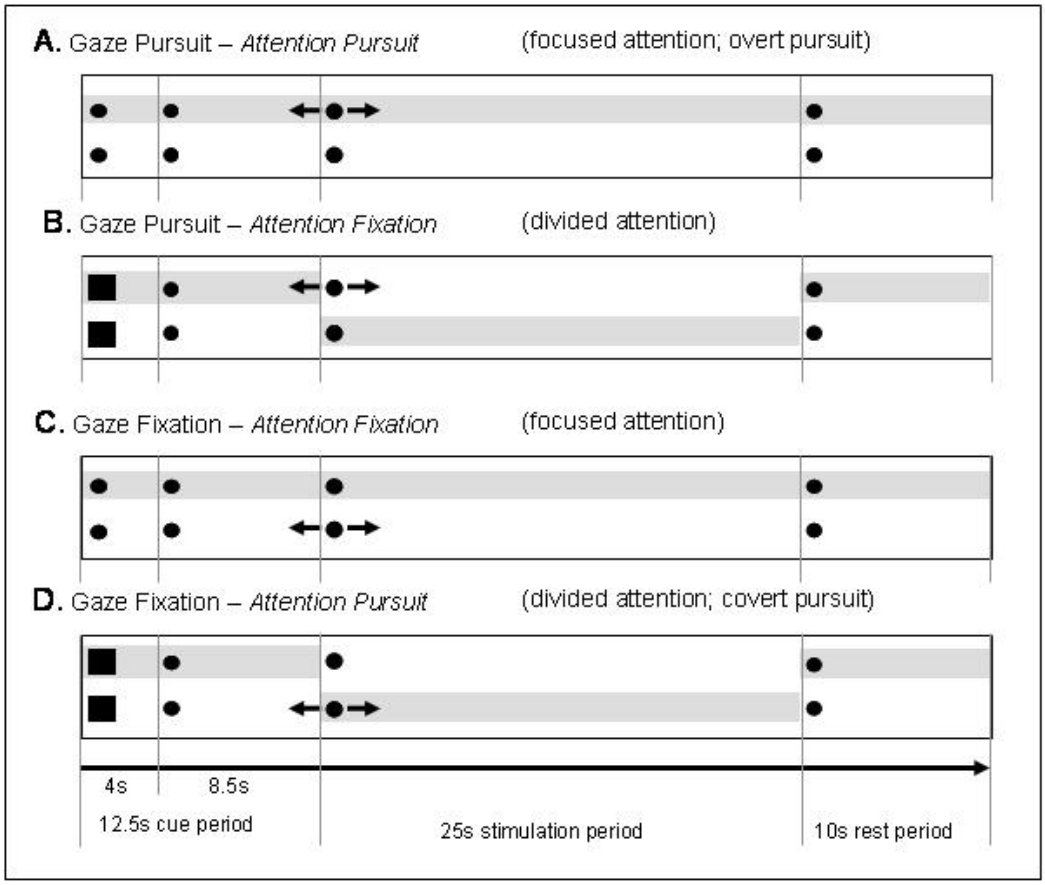

Fig.1 Schematic time course of experimental tasks A-D. Each trial started with a 12.5 s cue period, followed by 25 s of stimulation period, terminated by a 10 s rest period. Gaze always directed to the upper dot, likewise attention (attention locus indicated by shaded area, not shown in the experiment). If the squared cue appeared, attention had to be directed to the lower dot during the next stimulation sequence. Black arrows indicate sinusoidal motion in the horizontal plane during stimulation.

One stimulus condition was tested per trial. The four tasks (A-D) were repeated three times in a pseudo-random order resulting in 12 trials per series. Each subject performed 3 series.
Two instructions were given to the subjects prior to measurements in the MR-scanner: (i) "Always keep gaze directed on the upper dot during the whole experiment" (since subjects had their heads immobilized in the scanner, gaze direction was identical with eye direction), (ii) "Keep visual attention directed on the upper dot unless the cue appears (the two dots change to squares). If the cue does appear, covertly shift attention to the lower dot during the subsequent stimulation period and then shift attention back to the upper dot" (Fig. 1).
Note that we controlled for gaze direction, but not for attention direction. In this experimental approach we investigated whether the task to shift attention away from gaze is able to

modulate the cortical BOLD response. If differences occur they can at least in part be related to the process of dividing attention and gaze directions. Methods to control the attention direction (e.g. by prompting subjects to indicate random dimmings or colour changes of the attention target) have the disadvantage that they can only yield discrete samples of attention direction. Intermittent shifts of attention remain undiscovered and uncontrolled. In addition, such methods may cause popout effects, visual distraction etc. and thereby further complicate the paradigm.

To control for effects of the cue's change in form and size we applied an inverted task in a control experiment. In this inverted paradigm subjects always had to shift attention covertly to the lower dot during the stimulation period. If the cue appeared attention and gaze directions remained on the upper dot during the stimulation period.

Subjects were trained to perform the four tasks before fMRI measurements to assure that they correctly understood the tasks and the meaning of the cue. Training of the subjects, monitoring of eye movements during the scanning sessions, and interview after the scanning session assured that subjects performed the task correctly.

FMRI

Measurements were performed on a 1.5T Avanto (Siemens, Erlangen) MR Scanner. Functional imaging was performed with T2*-weighted gradient recalled EPI (echoplanar imaging) sequences (TR 2.5 sec., TE 50ms, Flip Angle 90°, field of view 22x22cm^2, matrix size= 64x64x28, voxel size 3.44 x 3.44 x 5mm^3). Anatomical images of the head and brain were obtained using high-resolution T1-weighted 1-mm isovoxel MP-RAGE (magnetization prepared rapid acquisition gradient echo) sequences (192 slices, TR= 2000ms, TE=3.22ms , field of view 25.6 x 25.6 cm^2, Flip Angle 8°, voxel size 1x1x1mm^3). Shimming was performed for the entire brain using an auto-shim routine for magnetic field homogeneity. The stimulation protocol for each stimulation sequence consisted of twelve 25 s stimulation intervals each preceded by a 12.5s cue period and succeeded by a 10 s period of rest. This protocol produced 228 EPI volumes per series. Each subject had to perform three series. Data acquisition was performed in 28 slices per volume containing the whole brain except the cerebellum. Thus, measurement time was little more than half an hour for each subject. Subjects had their heads immobilized in the MR-headcoil. Effects of the gradient noises were reduced by sound-dampening headphones.

Eye-tracking

Eye movement measurements were performed in parallel to the fMRI measurements using the Freiburg infrared MR Eye-tracker (methods in detail in Kimmig *et al.* (1999)). A multi-channel computer program (LabVIEW®, National Instruments, Austin, Texas, USA) was used to acquire and display the signals derived from the MR-Eyetracker. The sampling frequency was 1000 Hz, the best spatial resolution was 0.2° of visual angle. The stimulus position was displayed and recorded in parallel to the eye movement data. The MR-scanner provided a TTL-pulse at the beginning of each volume acquisition. This pulse was used to trigger both our stimulation and the eye movement acquisition programs. Calibration of eye position was performed prior and after each run. For calibration, subjects shifted their eyes repeatedly from the central fixation point towards targets at lateral locations of ± 5°.

Subjects

The study was approved by the Ethics Committee of the University of Freiburg and is consistent with the Declaration of Helsinki. Written informed consent was obtained from 12 healthy right handed subjects. Eight subjects participated in the experiment (3 males, 5 females). Four subjects performed exclusively the control experiment with the inverted cue task (2 males, 2 females). Age ranged between 24–35 years, vision was normal or corrected to normal. Right handedness was controlled using an adapted Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were compensated for participation in the study.

Data Analysis

FMRI data was analysed using the statistical parametric mapping software (SPM2) (http://www.fil.ion.ucl.ac.uk/spm/). Head motion was corrected via the realignment preprocessing tool of SPM2, data were spatially normalized to the MNI (Montreal Neurological Institute) EPI template brain and interpolated to 2x2x2 mm voxel size. Then data were spatially smoothed with a 6-mm isotropic Gaussian kernel, full width at half maximum. All brain activation findings are reported in the MNI coordinate system. Statistic analysis was performed using the general linear model of SPM2, group analysis was realized calculating a fixed effects analysis, in account to the subject quantity (n= 8). Main contrasts were calculated for each of the 4 stimulation conditions versus the rest condition *(*e.g. 'gaze pursuit *attention fixation'* – rest*)* and for the cue condition versus the rest condition. Differential contrasts (table 1) were calculated for gaze pursuit with divided vs. focused attention, for gaze fixation with divided vs. focused attention, for the cue condition vs. the gaze fixation conditions (cue - 'gaze fixation *attention fixation'* and cue - 'gaze fixation

attention pursuit'), attention pursuit vs. attention fixation and divided attention vs. focused attention tasks. All contrasts were family wise error (FWE) corrected. Activations with $p \leq 0.05$ were considered as being significant. Activation locations were identified via the SPM toolbox WFU pickatlas (Lancaster *et al.*, 2000; Tzourio-Mazoyer *et al.*, 2002; Maldjian *et al.*, 2003; Maldjian *et al.*, 2004).

We used the statistical parametric mapping software SPM2. Today SPM is the commonly known standard of brain data analysis, which allows for robust FWE corrected results. Due to the limited number of subjects in this study, the analysis is confined to a fixed effects SPM analysis. To assure that the results are not just the effect of too many degrees of freedom included in a SPM fixed effects analysis, we performed in addition a statistical nonparametric analysis (SnPM; uncorrected t-threshold of T=3; Holmes *et al.*, 1996). Nonparametric tests are generally more robust, but less sensitive than parametric tests and yield more distributed clusters of activation. However, both methods should reveal similar activations in the well-known regions of the smooth pursuit system.

Table 1 Stimulation conditions and differential contrasts

	Attention pursuit	Attention fixation	Differential contrast
Gaze pursuit	Focused attention (A)	Divided attention (B)	B - A
Gaze fixation	Divided attention (D)	Focused attention (C)	D - C
	Attention pursuit (A + D)	Attention fixation (B + C)	(A + D) - (B + C)
	Divided attention (B + D)	Focused attention (A + C)	(B + D) - (A + C)

For eye movement data analysis we used a semi automatic MatLab (The Math-Works Inc., Natick, MA, USA) based analysis program, with which we calibrated the data, detected saccades, blinks and artifacts. Then we calculated SPEM gain in the pursuit conditions (gain defined as ratio of eye velocity to target velocity), the mean saccade amplitude and the saccadic frequency in all stimulation tasks.

Results

Eye Movement Data

Original eye movement traces of the 'gaze pursuit *attention pursuit*' task and the 'gaze pursuit *attention fixation*' task are shown in Fig.2A,B. The performance of gaze pursuit was very good, even though attention was required to be directed away from the gaze pursuit target (Fig.2B). SPEM gain in both SPEM tasks was close to unity, indicating that subjects followed the moving dot accurately (Fig. 2C). There was no significant difference in SPEM gain in the 'gaze pursuit *attention pursuit*' task and the 'gaze pursuit *attention fixation*' tasks ($p > 0.9$). Saccades occurred at slightly higher frequency during gaze pursuit sequences than during rest and gaze fixation sequences, however without reaching statistical significance (Fig. 2D, $p > 0.12$). The saccade amplitude was significantly higher during pursuit (Fig. 2E, $F(2,7)=19.25$; $p < 0.0001$) as compared to rest and gaze fixation. These saccades were however very small in all conditions (max. 1.2° of visual angle). According to our previous study one would expect no effect for saccade amplitudes between 2-10°, and possibly no effect for the small amplitudes of about 1° (Kimmig *et al.*, 2001).

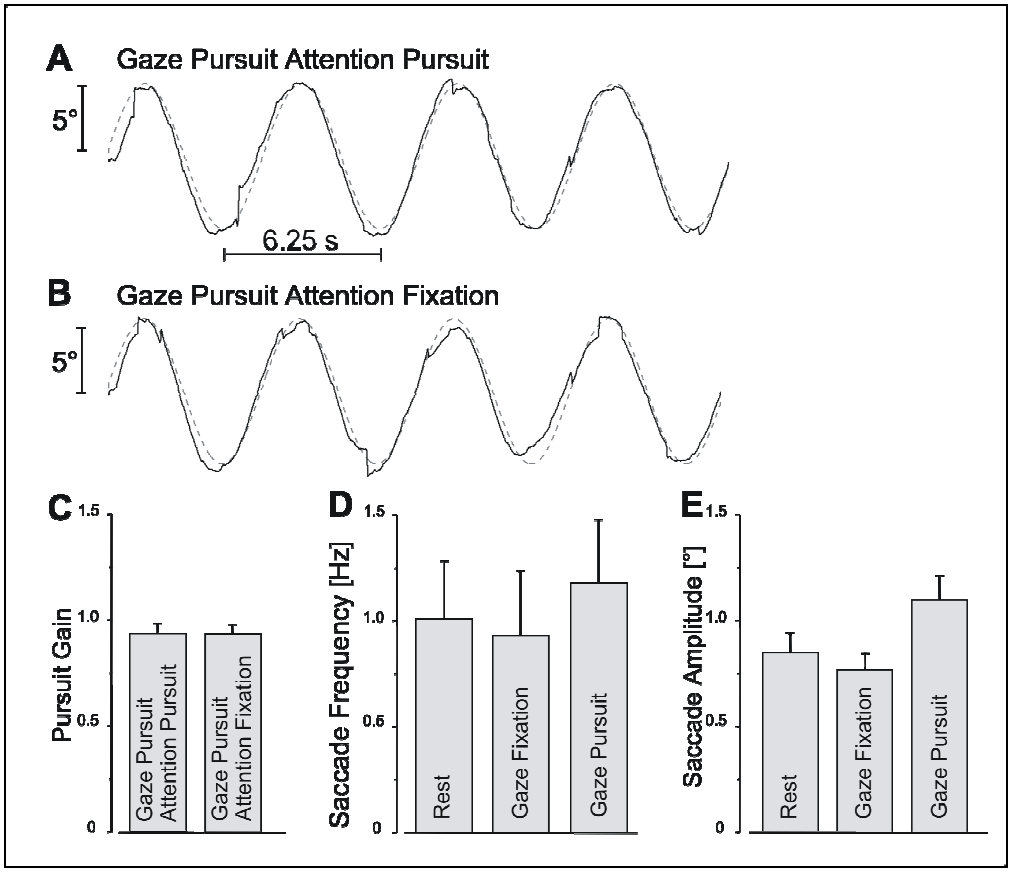

Fig.2 Eye movement data. (A) Original SPEM trace overlaid on sinusoidal stimulus signal (amplitude ±5°, frequency 0.16 Hz, peak velocity 5°/s). Gaze and attention direction focused on the stimulus. (B) SPEM following the same stimulus signal as in (A), but attention directed to a stationary target. (C) Gaze pursuit gain of n=8 subjects in the two pursuit tasks (A, B) close to unity, independent of attention direction. (D) Saccadic frequency in the rest, gaze fixation and gaze pursuit periods**.** Saccadic frequency during gaze pursuit was slightly, but not significantly higher than during rest and gaze fixation. (E) Mean saccade amplitude in the rest, gaze fixation and gaze pursuit periods. Generally, amplitudes were very small (about 1.2° of visual angle). N = 8. Error bars: standard error.

FMRI Data

Gaze pursuit with attention on the pursuit target ('gaze pursuit *attention pursuit*' - rest) activated the well-known pursuit network, cuneus, precuneus (PCU), MT+, PPC, posterior cingulate gyrus (pCG), SEF, FEF and the putamen as part of the basal ganglia (Fig. 3A; for an overview of local activation maxima see table 2). Covert shifts of attention (to the lower stationary dot) during SPEM ('gaze pursuit *attention fixation*' - rest) similarly activated cuneus, PCU, MT+, PPC, pCG, SEF, FEF and the putamen (Fig. 3B; table 2).

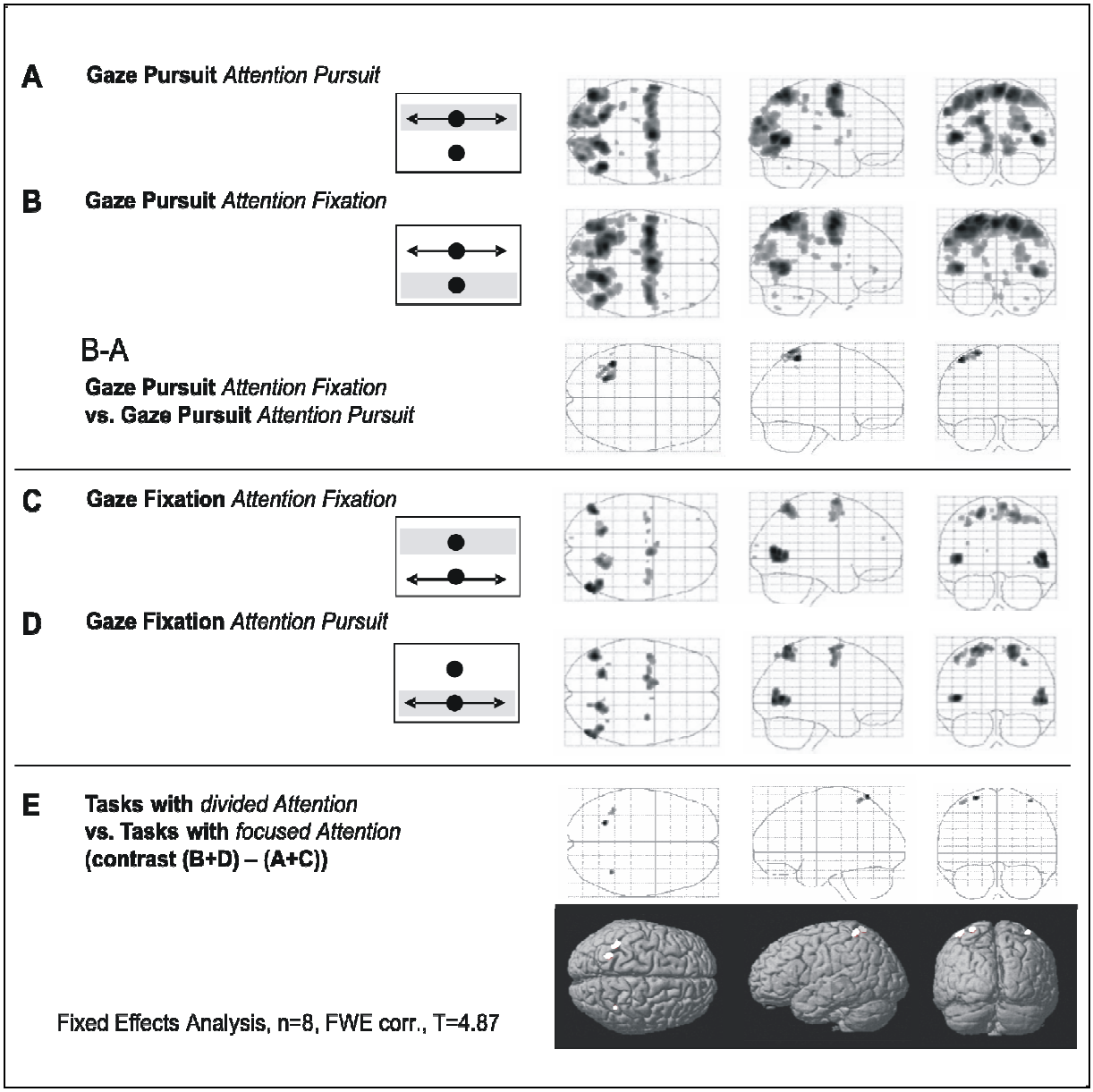

Fig.3 Functional data of 8 subjects shown by glass brains in the horizontal, sagittal and coronal plane for (A) 'gaze pursuit attention pursuit', (B) 'gaze pursuit attention fixation', the differential contrast B-A, (C) 'gaze fixation attention fixation', (D) 'gaze fixation attention pursuit', (E) the differential contrast divided attention – focused attention, (B+D) – (A+C). Insets delineate the stimulation setup: black arrows indicate sinusoidal motion of the corresponding dot. Shaded bars indicate attention location (not shown in the experiment).

To detect activation specifically related to the shift of ‘attention direction’ away from ‘gaze direction’ (i.e. the effect of divided attention) during gaze pursuit we calculated the difference contrast of ‘gaze pursuit *attention fixation*’ – ‘gaze pursuit *attention pursuit*’ (Fig. 3B-A; table 2), which revealed significant differential activations in the superior and inferior parietal lobule (IPL, SPL) and in the postcentral gyrus, predominantly in the left hemisphere.

Gaze fixation during motion of a peripheral dot with attention directed to the stationary fixation dot (‘gaze fixation *attention fixation*’ - rest; Fig. 3C; table 2) also activated parts of the SPEM network, namely MT+, PPC, FEF and SEF. However these activations were lower and more circumscribed than those during pursuit. Significant activations were not observed in primary visual areas, PCU, pCG and the putamen. A very similar activation pattern (MT+, PPC, FEF and SEF) was found during gaze fixation with attention directed to the moving lower dot (‘gaze fixation *attention pursuit*’ - rest; Fig.3D; table 2).

To investigate the effect of attention shifts away from gaze (i.e. the effect of divided attention) during gaze fixation we calculated the contrast of ‘gaze fixation *attention pursuit*’ – ‘gaze fixation *attention fixation*’ (Fig.3D-C). However, we did not observe any significant differential activation. Similarly, the differential contrast of both tasks with attention pursuit vs. both tasks with attention fixation (Fig.3 (A+D)-(B+C)) did not show significant activations.

Finally, the differential activation contrast of tasks with divided attention, ‘gaze pursuit *attention fixation*’ and ‘gaze fixation *attention pursuit*’ (Fig. 3B+D) vs. tasks with focused attention, ‘gaze pursuit *attention pursuit*’ and ‘gaze fixation *attention fixation*’ (Fig. 3A+C) showed activation in a part of the PPC in both hemispheres (Fig. 3E, table 3, diff. contrast (B+D) – (A+C)). Please note, that this contrast is independent of eye movements and therefore represents attention specific activation in terms of divided attention.

Table 2 Activation locations of the main contrasts- rest

Anatomical Area	Gaze Pursuit *Attention Pursuit*					Gaze Pursuit *Attention Fixation*					Gaze Fixation *Attention Fixation*					Gaze Fixation *Attention Pursuit*					Cue				
		Coordinates					Coordinates					Coordinates					Coordinates					Coordinates				
	BA /CR	X	Y	Z	T	BA /CR	X	Y	Z	T	BA /CR	X	Y	Z	T	BA /CR	X	Y	Z	T	BA /CR	X	Y	Z	T
R Superior Parietal lobe		16	-68	60	*9.82*		20	-62	64	*12.38*							18	-62	68	*7.28*		18	-72	60	*11.19*
	7	20	-60	64	*10.25*		16	-72	60	*11.33*		18	-60	*60*	*6.77*	7	18	-62	58	*7.20*		28	-62	62	*7.67*
						5	38	-50	64	*7.97*							24	-56	60	*6.65*					
L Superior Parietal lobe		-28	-56	58	*8.31*	7	-20	-56	70	*12.84*		-22	-56	60	*7.21*		-24	-58	66	*7.20*		-22	-58	68	*7.33*
	7	-20	-60	62	*10.25*		-34	-52	66	*11.29*		-30	-60	62	*5.28*		-18	-54	74	*5.48*	7	-18	-66	58	*7.28*
R Inferior Parietal lobe																						36	-50	52	*6.45*
R Middle Frontal Gyrus	6/FEF	32	-6	56	*8.22*						6/FEF	46	-6	52	*5.74*										
	6	40	-4	60	*8.08*						6/FEF	32	-4	54	*5.7*										
L Middle Frontal Gyrus							-28	-6	58	*11.38*						6/SEF	-18	-8	66	*6.77*		-28	-4	52	*9.48*
L Medial Frontal Gyrus						6/SEF	-2	-4	64	*12.56*												-4	8	50	*5.97*
R Superior Frontal Gyrus											6/SEF	6	-2	70	*6.83*										
L Superior Frontal Gyrus	SEF	4	-4	68	*10.85*						6/SEF	-4	4	56	*5.72*		-12	0	70	*6.29*					
												-20	-6	62	*5.42*	6/SEF	-6	-6	68	*6.15*		SEF	- 20	-2	72 *7.05*
R Precentral Gyrus	6	54	0	48	*6.12*																	6/FEF	28	-4	48 *6.71*
																							42	-4	48 *5.94*
L Precentral Gyrus	6	-42	-10	54	*8.92*		-40	-6	58	*12.87*	6	-42	-10	56	*5.32*						6/FEF	-44	-4	46	*5.84*
												-34	-6	50	*5.91*										
R Precuneus												10	-56	64	*5.60*										
L Precuneus		-12	-72	58	*7.83*		-16	-62	66	*11.51*												-12	-72	60	*8.35*
R Cuneus	17	16	-96	0	*6.93*		26	-76	32	*7.18*															
L Cuneus	19	-20	-92	28	*9.34*		-14	-92	16	*5.90*															
	18	-14	-94	16	*7.99*																				
R Lingual Gyrus		12	-72	-12	*7.21*		10	-72	-12	*5.89*															
		10	-70	0	*7.27*		10	-70	0	*5.67*															
L Lingual Gyrus	18	-10	-72	-6	*8.51*	18	-10	-70	-6	*6.32*															
L Postcentral Gyrus	40	-34	-38	60	*6.49*																				
		-30	-40	44	*6.13*																				
		28	-40	52	*5.53*																				
R Inferior Occipital Gyrus																					18	46	-78	-6	*6.58*
R Middle Temporal Gyrus							46	-62	0	*11.20*	39	52	-72	10	*8.47*		52	-76	2	*7.52*					
						39/V5	50	-72	10	*6.59*	37	54	-70	0	*8.09*		56	-68	0	*7.10*	37/V5	50	-68	2	*6.42*
												46	-60	4	*7.64*		52	-74	12	*6.98*					
L Middle Temporal Gyrus	39/V5	-48	-72	8	*10.84*		-44	-64	6	*11.42*	37	-46	-68	6	*7.98*										
		-50	-58	4	*7.18*	22	-54	-50	12	*5.39*															
R Middle Occipital Gyrus	39/V5	50	-74	10	*6.77*																				
		34	-84	20	*8.96*	19	34	-84	18	*7.40*												42	-84	6	*5.46*
		-34	-84	10	*5.43*																				
L Middle Occipital Gyrus						39	V5	-46	-74	8 *10.34*							-46	-66	4	*8.05*		-40	-74	6	*5.32*
R Superior Frontal Gyrus																					6	20	-8	70	*6.01*
R Superior Occipital Gyrus							26	-92	16	*6.47*															
L Supramarginal Gyrus		-54	-26	20	*5.83*		-48	-40	30	*7.10*															
							-54	-44	34	*6.04*															
							-56	-24	18	*5.89*															
L Putamen		26	-2	2	*5.68*		26	-2	6	*6.25*															
L Cingulate Gyrus		-14	-22	38	*5.43*		-14	-20	38	*6.85*															
R Inferior Frontal Gyrus		62	12	14	*5.35*	10	52	42	0	*6.54*															
L Fusiform Gyrus		-28	-74	-10	*5.32*																				

Voxel coordinates show the local maximum of an activated voxel cluster; BA = Brodmann Area; CR = Cortical Region; T = T-value at voxel-level; xyz = MNI coordinates.

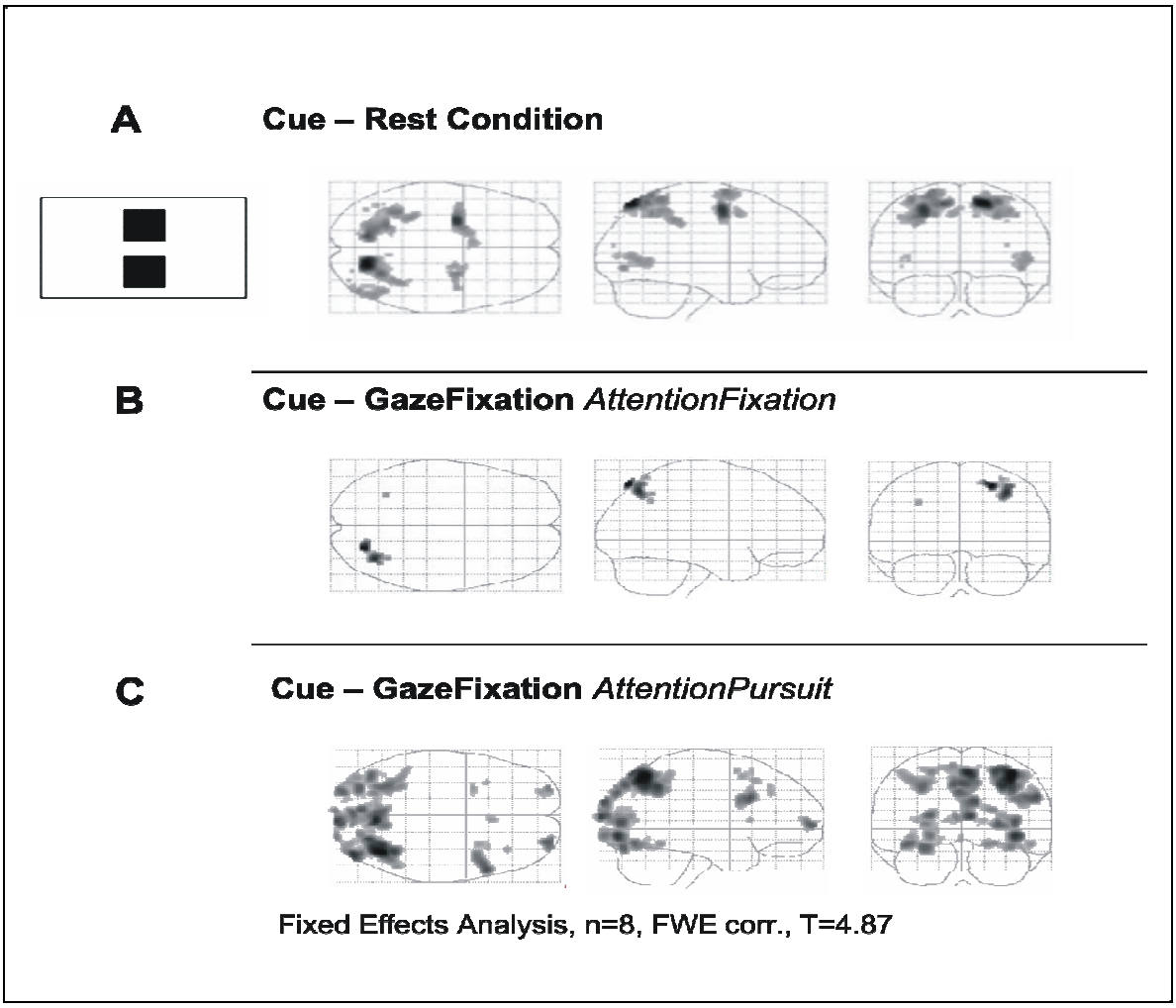

Fig. 4 Functional data of 8 subjects shown by glass brains in the horizontal, sagittal and coronal plane. (A) Effect of the task to divide attention and gaze directions in the subsequent stimulation period, cue - rest condition. (B) Differential contrast cue – 'gaze fixation *attention fixation*'. (C) Differential contrast cue – 'gaze fixation *attention pursuit*'.

We did not find attention related regions outside the well known visuo-oculomotor network.

The task of dividing attention and gaze directions during the next stimulation period (indicated by the cue) led to activation of PCU, MT+, PPC, FEF, and SEF already in the cue period (Fig. 4A, table 2).

The cue consisted in a change of the two dots from circles to somewhat larger squares. In the control experiment the squares indicated to the subject not to shift attention, which did not lead to any specific activation in the cue – rest contrast. Thus, the cue's change in form and size per se could not explain the activations related to upcoming attention shifts.

Table 3 Activation locations of differential contrasts

Anatomical Area	**Gaze Pursuit *Attention Fixation* vs. Gaze Pursuit *Attention Pursuit*** (contrast Fig. 3B-A)	***Divided Attention vs. Focused Attention*** (contrast Fig. 3 (B+D) – (A+C))	***Cue* vs. Gaze Fixation *Attention Pursuit***	***Cue* vs. Gaze Fixation *Attention Fixation***
	Coordinates BA X Y Z *T*	Coordinates BA X Y Z *T*	Coordinates BA X Y Z *T*	Coordinates BA X Y Z *T*
R Superior Parietal lobe		26 -50 74 *4.37*	36 -64 54 9.97 26 -72 58 8.15	24 -76 56 6.74 34 -68 50 6.33
L Superior Parietal lobe	-24 -56 70 *6.38* BA 7 -36 -58 64 *5.64*	-24 -58 70 *5.82* -30 -46 72 *4.27*	BA 40 36 -56 44 8.29	
R Inferior Parietal Lobe				34 -58 46 5.3
L Inferior Parietal lobe	-42 -48 62 *6.67* -54 -50 52 *4.93* -56 -42 52 *4.88*			-30 -58 40 5.26
R Postcentral Gyrus				
L Postcentral Gyrus		BA 5 -40 -48 64 *5.15*		
R Precuneus			4 -68 56 9.02	
R Cuneus			BA 18 6 -98 12 8.17 BA 23 16 -74 8 5.45	
L Cuneus			-24 -96 -6 6.88	
R Inferior Occipital Gyrus			40 -86 -6 8.77	
L Middle Occipital Gyrus			-24 -94 14 7.38 -36 -90 10 5.18 -40 -72 -14 7.35	
L Fusiform Gyrus			-28 -82 -18 7.38	
R inferior Frontal Gyrus			56 16 32 7.94 42 8 30 6.82	
R Superior Frontal Gyrus			BA 10 28 62 6 7.42 30 10 54 5.73 BA 8 32 18 58 5.34	
L Superior Frontal Gyrus			-28 64 6 6.5 BA 10 -20 62 0 5.49	
R Inferior Frontal Gyrus			56 16 32 7.94 42 8 30 6.82	
R Middle Frontal Gyrus			34 32 38 5.66	
L Middle Frontal Gyrus			-28 6 60 5.79	
R Medial Frontal Gyrus			BA 8 4 20 50 5.8	

Voxel coordinates show the local maximum of an activated voxel cluster; BA = Brodmann Area; T = T-value at voxel-level; xyz = MNI coordinates.

The differential contrast cue – ‘gaze fixation *attention fixation*’ showed activation in a more lateral part of PPC (Fig.4B; table 3). The differential contrast cue – ‘gaze fixation *attention pursuit*’ yielded similar activations in PPC, but additional activations in PCU, striate cortex, FEF, SEF and the superior frontal gyrus (BA 10) (Fig.4C; table 3).

As expected, the SnPM analysis revealed more scattered clusters of activation. The analysis showed activations in the well known regions of the SPEM network, but also scattered activations in un-hypothesized brain regions. An overview of the activated clusters resulting from the SnPM analysis is given in tables 4 and 5. In the regions of interest for SPEM, the results corresponded with those of the SPM analysis, with respect to the main contrasts as well as to the differential contrasts. Therefore, we will focus the discussion on these regions. Scattered activations found solely by the SnPM analysis in un-hypothesized regions may be found in the table, but will not be discussed further given uncertainties about their neurobiological relevance.

Table 4 Activation locations of SnPM main contrasts (stimulation vs rest)

Anatomical Area	GazePursuit AttentionPursuit vs. Rest						GazePursuit AttentionFixation vs. Rest						GazeFixation AttentionFixation vs. Rest						GazeFixation AttentionPursuit vs. Rest						Cue vs. Rest					
	BA –Area	Voxel coord.			Cluster	pT-Value	BA –Area	Voxel coord.			Cluster	pT-Value	BA-Area	Voxel coord.			Cluster	pT-Value	BA-Area	Voxel coord.			Cluster	pT-Value	BA –Area	Voxel coord.			Cluster	pT-Value
		X	Y	Z				X	Y	Z																X	Y	Z		
L Superior Frontal Gyrus													BA 8	-40	18	54	22	4,1												
														-30	-2	68	15	3,7												
													BA 6 (SEF)	-6	6	56	16	3,49												
R Middle Frontal Gyrus	BA6 (FEF)	32	-6	52	387	4,72	BA 6 (FEF)	36	-8	48	524	5,08							BA6	32	-8	48	22	3,55		30	-6	50	381	5,78
							BA 6 (FEF)	42	-6	54	524	4,72																		
L Middle Frontal Gyrus	BA6 (FEF)	-28	-8	52	1062	4,88	BA 6 (FEF)	-28	-8	52	1897	5,37	BA 10	-36	52	26	21	3,7	BA 6	-40	-2	60	7	3,35	BA 6	-28	-6	54	614	6,13
													BA 6	-34	-6	48	25	3,41	BA 6 (FEF)	-26	-6	48	3	3,04	BA 6	-44	0	38	614	4,25
R Medial Frontal Gyrus	BA 6 (SEF)	2	-4	62	1062	4,95																								
L Medial Frontal Gyrus		-10	-10	62	1062	4,27	BA 6 (SEF)	-2	-2	62	1897	5,58																		
L Inferior Frontal Gyrus							BA 44	-54	12	18	149	4,77														-52	8	16	30	3,99
R Precentral Gyrus	BA6	40	-10	48	387	4,66								36	0	-50	8	3,97												
		42	-6	58	387	3,94																								
L Precentral Gyrus								-44	-6	56	1897	4,84	BA 6	-50	-6	54	53	3,95							BA 6	-36	-4	46	614	46
L Postcentral Lobe		-30	-40	44	32	4,02																								
R Superior Parietal lobule								18	-64	66	400	4,15							BA 7	18	-60	68	19	3,49	BA 7	22	-72	58	2440	5,53
L Superior Parietal lobule		-22	-58	56	373	5,23							BA 7	-22	-56	58	153	4,93	BA 7	-26	-58	60	16	3,46	BA 7	-12	-72	58	2240	5,18
	BA 7	-12	-72	58	373	4,15																								
L Inferior Parietal lobule								-30	-38	42	362	5,08		-30	-44	46	19	3,43							BA 40	-34	-50	50	2440	5,46
								-30	-48	52	362	4,44																		
R Precuneus		24	-56	54	70	4,39	BA 7	22	-56	54	400	5,54		22	-52	54	282	4,63	BA 7	20	-54	54	4	3,14						
							BA 7	14	-48	52	400	4,5																		
L Precuneus		-24	-78	26	96	3,91	BA7	-20	-56	54	362	3,89																		
		-16	-70	38	96	3,19																								
R Cuneus	BA 19	24	-78	30	265	3,63																								
L Lingual Gyrus	BA 18	-10	-70	-6	116	4,43																								
R Middle Temporal Gyrus	BA 37 (MT+)	44	-62	4	156	4,65	BA 39 (MT+)	42	-58	6	315	4,98		44	-60	4	319	4,17		46	-60	2	19	3,4		44	-60	2	324	4,78
L Middle Temporal Gyrus							BA 39 (MT+)	-42	-60	6	433	5,4	BA37 MT+	-44	-66	6	80	3,86	BA37 (MT+)	-44	-66	6	22	3,47	BA 37 (MT+)	-42	-66	4	387	4
																										-46	-60	-4	387	4
R Middle Occipital Gyrus	BA 19	34	-84	18	265	5,02							BA 19 (MT+)	48	-78	-8	319	5,41							BA 19 (MT+)	48	-72	6	324	3,81
		32	-74	26	265	3,52																				36	-86	18	35	4
L Middle Occipital Gyrus	BA 37 (MT+)	-42	-72	6	152	4,1																				-38	-74	6	387	5,11
R Inferior Occipital Gyrus																										46	-80	-6	50	4,83
L Inferior Occipital Gyrus																														
R Inferior Temporal Gyrus													BA 37 (MT+)	54	-72	-2	319	5,18												
R Putamen		26	0	2	279	4,83		26	0	6	456	5,9																		
L Cingulate Gyrus								-14	-20	38	92	4,83								22	6	38	13	3,87						
L Lat Glob Pall								24	-12	-4	456	3,91																		

Coordinates show the local maximum of an activated voxel cluster in MNI spac; fR = functional region; pT = pseudo T-value at voxel level.

Table 5 Activation locations of SnPM differential contrasts

Anatomical Area	**GazePursuit AttentionFixation vs. GazePursuitAttentionPursuit**						**Divided Attention vs. Focused Attention**						**Cue vs. GazeFixation *AttentionFixation***						**Cue vs. GazeFixation *AttentionPursuit***					
	BA –Area	Voxel coord. X	Y	Z	Cluster	pT-Value	BA –Area	Voxel coord. X	Y	Z	Cluster	pT-Value	BA-Area	Voxel coord.			Cluster	pT-Value	BA-Area	Voxel coord.			Cluster	pT-Value
R Middle Frontal Gyrus																			BA 9	50	14	32	246	4,55
L Medial Frontal Gyrus								-8	52	-8	10	3,31												
R Inferior Frontal Gyrus		32	8	30		4,05							BA46	52	28	20	5	3,24		38	8	30	246	4,05
R Postcentral Gyrus							BA 5	30	-48	72	68	4,39												
L Postcentral Gyrus																								
R Superior Parietal lobule	(BA5)	38	-48	66		4,38	BA5	38	-50	66	68	4	BA 7	30	-68	60	254	4,48	BA7	38	-64	56	1062	7,03
													BA7	32	-66	46	254	3,45		30	-66	44	1062	4,61
L Superior Parietal lobule							BA 7	-26	-56	70	131	4,37		-40	-50	62	19	3,59		-22	-72	58	804	4,89
								-26	-44	74	131	4,09												
R Inferior Parietal lobule		34	-46	58		3,24								46	-58	56	254	3,22		36	-54	42	1062	5,05
L Inferior Parietal lobule		-20	-14	56		4,25																		
	BA 40	48	-40	60		3,31																		
R Supramarginal Gyrus													BA 40	62	-48	36	17	3,26						
R Precuneus																				10	-76	56	804	4,47
L Precuneus							BA 7	-18	-44	78	131	3,61		-6	-66	66	9	3,38						
R Cuneus													BA19	6	-92	32	14	3,56	BA 19	6	-94	30	804	4,57
L Cuneus																				-30	-90	25	127	4,57
R Middle Occipital Gyrus														28	-62	2	14	3,61	BA 19	40	-82	6	175	4,56
L Middle Occipital Gyrus																				-24	-92	14	127	4,57
L Inferior Occipital Lobule														-40	-58	-10	30	4,25		-40	-62	-8	156	4,02
R Lingual Gyrus														26	-94	-16	22	4,55						
R Cingulate Gyrus	BA 24	-14	-6	50		3,55	BA24	8	32	14	52	3,7		10	-8	30	10	3,41						
L Fusiform Gyrus														-28	-80	-18	50	4,22	BA 19	-44	-70	-18	156	4,83
L Insula		-36	8	6		3,76								-34	14	10	14	3,63		-32	16	10	99	4,45
L Thalamus		-2	-12	12		5,35																		

Coordinates show the local maximum of an activated voxel cluster in MNI spac; fR = functional region; pT = pseudo T-value at voxel level.

Discussion

This is the first fMRI study to investigate the effects of dissociating visual attention and gaze directions during smooth pursuit eye movements, simulating natural behaviour of attention shifts to objects in motion. Our intention was to describe those parts of the brain that control visual attention during smooth pursuit eye movements.

Gaze pursuit with focused vs. divided attention

Our data showed that gaze pursuit with the task to divide attention from gaze direction was as good as gaze pursuit with the task to focus attention on the gaze direction. Two explanations can be given for this oculomotor result, 1) visual attention can indeed be divided from gaze during smooth pursuit eye movements without significant changes of gaze pursuit performance, or 2) subjects did not execute the task correctly, such that attention and gaze directions remained focused in both the 'gaze pursuit attention pursuit' and the 'gaze pursuit attention fixation' tasks.

Irrespective of the tasks to divide or to focus attention and gaze directions, our fMRI data revealed that SPEM always activated a similar cerebral network. However, the gaze pursuit task with divided attention led to a general tendency of more cortical activation in the whole SPEM system, and significantly higher activations in the left posterior parietal cortex (SPL, IPL, postcentral gyrus; contrast Fig.3B-A). Thus, additional processing appeared to be required for the task to shift attention to a stationary target while maintaining gaze pursuit. Our data indicate that subjects tried to divide attention and gaze directions during gaze pursuit. This attempt did not influence gaze pursuit performance. The additional cortical processing might be due either to the effort to keep gaze and attention directions divided, to switching the attention focus repeatedly between the two targets, or to the suppression of saccades to the stationary target.

Previous studies investigating focused attention vs. distributed or divided attention during fixation tasks also described an increased parietal activity for divided attention (Jovicich *et al.*, 2001; Nebel *et al.*, 2005; Sturm *et al.*, 2006). The study of Jovicich et al. (2001) even demonstrated a correlation between the number of attention targets and the amount of PPC activation. Yantis et al. (2002) concluded from their data that activation in posterior parietal cortex was of transient nature and correlated to the shift of attention, not to maintaining attention at a defined location. Hemispheric differences should not be overestimated in our data set. Shulman et al. (2002) reported stronger activations in the left PPC during preparation (cue period) and execution (test period) of attention tasks of different dimensions or motion direction. Furthermore, attentional switching between global and local aspects of

visual stimuli led to activation of the left medial parietal cortex (Fink *et al.*, 1997). Gitelman et al. (1999) on the other hand reported more activation in the right parietal cortex during attention shifting to the right and left visual hemifield.

Gaze fixation with focused vs. divided attention

Furthermore, we found that the task to attend to a moving target while fixating a stationary target activated the same cortical network as did pursuit eye movements (FEF, SEF, PPC, MT+; Fig.3D). Essentially the same result was obtained when both attention and gaze directions had to be kept on the stationary target (Fig.3C) while a second target was moving. One interpretation of the latter result is that our subjects were in fact not able to keep attention on the 'boring' stationary target, but inevitably shifted attention to the moving target. A more complex explanation would be that some of the regions are active independent of the attentional state or that different functions are processed within the same region (e.g. fixation/suppression of eye movements vs. execution of eye movements within FEF).

Attention pursuit vs. Attention fixation

Both the attention pursuit tasks (Fig. 3; A and D) as well as the attention fixation tasks (Fig. 3; B and C) consist of a gaze pursuit and a gaze fixation task. The differential contrast (Fig. 3; (A+D)-(B+C)) is therefore independent of eye movements. Furthermore, both gaze pursuit conditions (Fig. 3; A and B) led to strong activations, compared to which the activations in the gaze fixation tasks (Fig. 3; C and D) were rather small. This might partially explain that the differential contrast of attention pursuit tasks vs. attention fixation tasks (Fig. 3; (A+D)-(B+C)) revealed no significant activations. We further concluded that neither attention pursuit nor attention fixation activated cortical regions outside the SPEM system, but instead attention pursuit and attention fixation seemed to be processed by similar cortical areas within the SPEM system. Similar mechanisms seem also to subserve the saccadic system, as previously shown.

Culham et al. (1998) showed that during fixation of a stationary target attentive tracking and attentive 'saccadic' shifts activated the same cortical regions, IPS, postcentral sulcus, SPL, cuneus, FEF and precentral sulcus. However they did not investigate attention directly during SPEM. While our task enables pursuit-like attentive tracking during SPEM, our activations were yet similar to those described by Culham et al. (1998). This indicates that attentive processes related to saccade-like shifts and to pursuit-like tracking operate in the same cortical structures.

Divided vs. focused attention (independent of eye movements)

Interestingly, when calculating the contrast specifically related to attention shifts (independent of gaze pursuit or gaze fixation) we obtained activation exclusively in the posterior parietal cortex. Such a contrast was not calculated in previous studies which mostly compared covert shifts of attention and saccades or attentive vs. passive viewing thereby modulating the cortical visuo-motor system as a whole. Furthermore, effects evoked by eye movement suppression could not be excluded by such previous designs (Culham *et al.*, 1998; Perry & Zeki, 2000; Beauchamp *et al.*, 2001; Yantis *et al.*, 2002). Our result is furthermore in accordance with the study of Wojciulik & Kanwisher (1999), which stated that posterior parietal areas around the IPS play a general role in visual selective attention independent of the kind of the attentional task.

Note that we did not find attention related regions outside the well-known visuo-oculomotor network.

Overt and covert pursuit

The 'gaze fixation attention pursuit' task (covert pursuit) activated similar cortex regions as the 'gaze pursuit *attention pursuit*' task (overt pursuit). This result indicates that overt pursuit and covert pursuit are processed by similar neural mechanisms. These mechanisms seem also to subserve the saccadic system (Corbetta *et al.*, 1998; Beauchamp *et al.*, 2001). Furthermore, the activations of the overt pursuit task were stronger than those of the covert pursuit task, a further analogy to overt and covert saccadic shifts (Beauchamp *et al.*, 2001). Taken together, our data indicate that the premotor theory of attention (Rizzolatti *et al.*, 1987) may also be applicable to the pursuit system.

Cortical processing in the cue condition

Furthermore, we found that most parts of the network active during SPEM could also be activated in the cue period (i.e. during fixation of a stationary target) by the simple task to divide attention and gaze directions during the subsequent stimulation period. This task led to bilateral activations of FEF, SPL, IPL, PCU and MT+. It remains undetermined whether these activations were due to attentional load or the preparation of the attention shift, to the suppression of eye movements or to untimely execution of the attention shift during the cue period. Among preparatory processes visuospatial short-term memory might play a role (i.e., subjects had to keep in mind the task of dividing attention and gaze directions during the following stimulation period). It has been reported that posterior parietal and prefrontal regions are involved in the retention of visuospatial information (Munk *et al.*, 2002; Todd &

Marois, 2005). Furthermore, similar activations as in our experiment were found during attention shifts, preparation of saccades and preparation of pointing hand movements following a cue indicating target location (Hopfinger *et al.*, 2000; Astafiev *et al.*, 2003). Chawla et al. (1999) reported that baseline activity in the motion sensitive area MT+ was enhanced by selective attention to the attribute 'motion' (even without a moving stimulus). These authors favoured the hypothesis that attention modulates sensitivity of neuronal populations to inputs by changing background activity.

Finally, the activations of the cue condition are different from those evoked by the gaze fixation conditions. The 'cue – gaze fixation attention fixation' contrast showed a higher activation in the PPC, predominantly of the right side. A similar result was obtained in the 'cue – gaze fixation attention pursuit' contrast, which in addition yielded activations in other regions of the SPEM network (like precuneus, primary visual areas, FEF). It seems that preparing to divide attention from gaze directions takes higher efforts than actually executing the task. In the latter differential contrast, area BA10 in the prefrontal cortex appeared active on both sides. Previously it has been shown that the frontal polar cortex of BA10 participates in sustained control processes, and plays a role in forming and maintaining an attentional set or task mode (Koechlin *et al.*, 1999; Sakai & Passingham, 2003; Velanova *et al.*, 2003). This seems to be important in the cue condition, but becomes irrelevant during execution of the task in the 'gaze fixation attention pursuit' condition.

In conclusion, our study shows that the modulation of visual attention is fully integrated in the cortical oculomotor network processes. Attention modulations operate within this network; as a kind of superordinate system they are independent of eye movements, but if eye movements are present attention modulations act on pursuit and saccades in a similar way. The process of dividing attention from gaze and its preparation is specifically controlled by the posterior parietal cortex. Whether, in a divided attention task, continuous attentive tracking is at all possible or whether attention is inevitably shifted between the attention targets remains to be shown in future studies.

Abbreviations

BA, Brodmann area; BOLD, Blood Oxygen Level Dependency; EPI, echoplanar imaging, FEF, frontal eye fields; fMRI, functional magnetic resonance imaging; FEW, family wise error; IPL, inferior parietal lobule; MNI, Montreal Neurological Institute;
MT+, motion sensitive region; pCG, posterior cingulate gyrus; PCU, precuneus; PET, positron emission tomography; PPC, posterior parietal cortex; SEF, supplementary eye fields; SnPM, statistical non-parametric mapping; SPEM, smooth pursuit eye movements; SPL, superior parietal lobule; SPM, statistical parametric mapping

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Chapter 4

Optic flow stimuli in and near the visual field centre: a group fMRI study of motion sensitive regions

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Abstract

An important region for cortical processing of visual motion is the MT+ complex in the parieto-occipito-temporal junction. Two subregions have been identified in humans, corresponding to the regions MT and MST, known from monkey studies. Human MT was activated by motion stimuli in the contralateral visual field, while MST responded to motion in both the contra- and ipsilateral field. Most functional imaging studies on motion processing focused exclusively on the MT+ complex, investigated few subjects and presented single subject maps of MT+. The stimuli consisted of mid to high velocity motion stimuli at large eccentricities from the mid-line. In this functional magnetic resonance imaging (fMRI) study we investigated whole brain activations in a group of healthy humans and performed a second level analysis. We tested the MT+ complex and its subdivisions in the low velocity range applying optic flow stimuli in and near the visual field centre.

We identified two subregions within the MT+ complex on group level. One subregion was activated by ipsi- and contralateral stimulation (supposedly MST) and located in the anterior part of MT+. A second subregion was exclusively activated by contralateral stimulation (presumably MT) and located in the more posterior part of MT+. The primary visual cortex was activated exclusively by motion in the contralateral field, but not by central flow fields. The interactions between MT and MST seemed to function properly even at low stimulus velocities. Furthermore, the eccentricity of the flow field relative to the midline played a minor role for the location of the MT+ subregions. This result questions the assumed size of MT receptive fields in humans. The particular role of the primary visual cortex in motion processing has to be elucidated in further studies.

Keywords

functional imaging - MT+ (MT/MST) subregions - hemifield – visual cortex

Introduction

The motion sensitive region MT+ with its middle temporal (MT) and medial superior temporal (MST) subareas has been extensively studied in monkeys [8-14]. The human homologue of MT+ has been identified by positron emission tomography [15;16] and fMRI studies [17-20]. Human MT+ is located on the ascending limb of the inferior temporal sulcus.

However, until to date few fMRI studies investigated the MT+ subdivision in MT and MST, their locations, size and functional properties. Subarea MT has been shown to be located in a more posterior part and subarea MST in a more anterior part of the MT+ complex. Morone et al. [21] identified a ventral subarea of the MT+ complex which was especially sensitive to direction changing optic flow. Brandt et al. [22] showed that only a small subarea of MT+ was activated during rotation stimulation of the ipsilateral visual hemifield. Dukelow et al. [23] and Huk et al. [24] identified subarea MT which was exclusively activated by contralateral flow field stimulation, MST however was activated by ipsilateral and contralateral stimulation. Furthermore, MT but not MST seemed to respond to retinotopic stimulation [25]. Smith et al. [26] found human MST to be strongly specialized for encoding global flow properties, while MT was less so. In monkey, MST is also known to receive extraretinal information during smooth pursuit eye movements [27-29]. This function was confirmed in humans by a study investigating non visual pursuit [23]. Goosens et al. [30] showed that two specific subareas of the MT+ complex, (one located partly in MST), get SPEM information. A subarea of MST was presumed to transform optic flow into head centric flow. To explain the effect that MST was activated by contralateral as well as ipsilateral stimulation while MT responded exclusively to contralateral stimulation, it is usually referred to the different receptive field sizes of MT and MST neurons found in monkey studies. In monkey, MT neurons were shown to have small receptive fields (RF). RF of MT neurons close to the midline expanded about 10-15° into the ipsilateral visual field [31;32], while MST neurons with large RF covered most of the ipsilateral field.

All cited human fMRI studies measured peripheral large field stimulations with medium to fast velocity flow fields or rotational motion during central fixation without measuring eye movements in the scanner. Furthermore, most of the human fMRI studies investigated few subjects (n = 4-9) with considerable intersubject variability, so that the data analysis was limited to the presentation of single subject maps of MT+. An inference on the population level was not possible. Furthermore, it remained unknown whether and how hemifield motion stimuli at low eccentricity and low velocity activate the MT+ complex.

In this study we measured cerebral activations in a large sample of subjects and performed a random effects analysis (RFX), which largely compensates for interindividual differences and allows for a more generalized interpretation of the data. We investigated how ipsilateral motion stimuli close to the center of the visual field activate the MT+ complex using low velocity flow field stimuli.

Material and Methods

Visual Stimulation

Visual stimuli were programmed using Matlab (The Mathworks, Natick, USA) in combination with Cogent Graphics (developed by J. Romaya, at the LON at the Wellcome Department of Imaging Neuroscience, UK) and back-projected onto a transluminent screen via an LCD-projector (NEC MT 1050, Tokyo, Japan). The screen was placed in the gantry at a distance of 75 cm to the subjects' eyes (30° x 23° of visual angle). Subjects saw the visual stimulation via a mirror which was mounted on the MR-headcoil. The stimulation paradigm was based on the one described by Huk et al. [33]. Stimuli consisted in alternating moving and stationary dot patterns of circular shape.

MT+ localizer stimulus

To localize MT+ a red fixation dot was projected in the centre of the screen (Ø 0.3° of visual angle). Subjects had to fixate this central dot during the whole scanning session (7.5 min). White dots (n=150; Ø 0.3°) were randomly distributed in a circular area (radius 8°). In the rest condition, the white dots remained stationary (duration 15s). In the stimulation condition (duration 15s), the dots moved radially from appearance at the centre of the flow field to disappearance at the pattern periphery with increasing speed of 0.5 to 4.2°/s (mean velocity 2.5°/s), and changed direction once per second. The dot pattern was spared around the fixation dot (min. radius 1.2°; Fig. 1A).

Ipsilateral stimulus

To separate MT and MST (according to their different responses to contra- and ipsilateral field stimulation) the circular dot pattern was located either in the right or left visual hemifield (offset of center of the circular pattern from the mid-line 8°; max. radius of the dot pattern 6°; min. radius 1.2°, shortest distance from the dot patch to the fixation dot, 2°; amount of white dots = 113; Fig. 1B, C). In the stimulation condition, we used the same velocity profiles as in

the localizer task. The rest conditions corresponded to the right and left hemifield stimulations, but the dots remained stationary.
These pairs of stimuli occurred in a pseudo randomized order. Each stimulation type and its rest condition (Localizer stimulus, ipsilateral stimulus +8°, ipsilateral stimulus -8°) were repeated five times in the fMRI session (duration 7.5 min).

MR Eye-tracking

For eye movement recordings we used the Freiburg MR-Eyetracker system, a fiber-optic limbus tracking device [34]. A multi-channel computer program (LabVIEW®, National Instruments, Austin, USA) recorded the eye movement data. The sampling frequency was 500 Hz, the spatial resolution 0.2° of visual angle.

MR-Imaging

Magnetic resonance imaging was performed with a 3 Tesla Magnetom TRIO scanner (Siemens, Erlangen, Germany). Functional imaging was performed with T2*-weighted echo-planar imaging (EPI) sequences which were equipped with fully automated distortion correction [35]. High-resolution, sagittal T1-weighted images were acquired with the MP-RAGE (magnetization prepared rapid acquisition gradient echo) sequence to obtain a 3D anatomical scan of the brain. The technical data for the functional measurements were TE 30 ms, TR 2.5 s, flip angle 90 °, field of view 192 * 210 mm^2, matrix 64 x 70, voxel size $3*3*3mm^3$. The stimulation protocol consisted of thirty 15s intervals including 15 periods of rest (OFF) and 15 periods of stimulation (ON). This protocol produced 180 echo planar volumes in one series (duration 7.5min). Data acquisition was performed in 36 slices per volume containing the whole brain excluding the cerebellum. To minimize head motion, the subject's head was fixed in the MR headcoil. Gradient noises were reduced by sound-dampening headphones.

Subjects

Eighteen healthy subjects (17 right handed and one left handed, age range 18–35 years) were included in the data analysis. Subjects' vision was normal or corrected to normal. Written informed consent was obtained from all subjects. The study was approved by the local Ethics Committee of the University of Freiburg.

Eye movement data analysis

Since visual stimulation in this experiment did not include any tasks of eye movements but required exclusively fixation of a stationary dot, the eye movement data were used to control for the subjects' vigilance and permanent fixation of the central dot.

FMRI data analysis

FMRI data were analyzed by use of the software package SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Residual head motion was corrected via SPM5 realignment. For multiple comparisons we normalized the EPI volumes using white and gray matter segmentation parameters of the anatomical T1 image. Spatial smoothing was performed with Gaussian spatial kernels of 8 mm (full width at half maximum). For statistical analysis data were fitted to a general linear model to establish parameter estimates for each subject.

We defined the main contrast for the MT+ localizer condition. For the ipsilateral conditions we defined main contrasts for stimulation of both the left and the right visual hemifield (all conditions were calculated moving dots – stationary dots) on a single subject level. For group comparisons we included the resulting main contrast images into three random effects one sample t-tests and corrected for multiple comparisons using family wise error (FWE) correction. Clusters of adjacent voxels surpassing an individual threshold of $p=0.05$ (corrected) were considered as significant activations.

For visualization purposes we projected the functional group results onto the left and right hemispheres of the human Colin surface-based atlas mapped to PALS ('Population-Average Landmark- and Surface-based'-atlas; [36-38]). Data were mapped on the flatmap template and the three dimensional cortical template of the atlas. This was done using the Computerized Anatomical Reconstruction and Editing Toolkit (CARET) version 5.3 (http://brainvis.wustl.edu) [39]. Statistical representations of the three main effects were mapped to different colours in functional overlays. Co-activated regions were displayed by weighted additive colour while pure colours indicated regions activated by only one of the tasks (localizer stimulus – blue; ipsilateral stimulus – red; contralateral stimulus – green; intensity scale 0 – 255 referring to the maximum activation of each contrast). Note that the flatmaps were only used for purposes of visualization of activation locations. They exclusively show grey matter activations surpassing a minimum threshold of $T = 6$ without considering effect size differences of stimulation tasks.

We report all findings in the MNI (Montreal Neurological Institute) coordinate system. Activation localization was performed via the SPM5 tool 'wfu pickatlas' [40;41]. Cerebellar and brainstem activations were not included in the statistical analysis.

Results

Eye movement data

During the whole experiment subjects fixated the center dot correctly and did not make any saccades to the stimuli shown in the left or right visual hemifield. Small corrective saccades or drifts below 0.5° occurred rarely during the scanning session.

FMRI data

The localizer stimulus led to bilateral activations in the medial occipital gyrus and middle temporal gyrus, corresponding to the MT+ region on group level (random effects group analysis, one sample t-test; FWE corrected; table1; Fig. 1A). Furthermore, we found activations in the cuneus, precuneus (lateral occipital sulcus (LOS) and V8) and very small activation in the inferior parietal lobule.

Table 1A

Anatomical Area	Localizer Stimulus vs. Rest					
	BA –Area/fR	Voxel coord.			Cluster	T-Value
		X	Y	Z		
R Middle Temporal Gyrus	BA 37 (MT+)	51	-69	3	222	13.5
		45	-60	3	222	10.3
L Middle Temporal Gyrus	BA 39 (MT+)	-45	-63	9	94	11.8
R Middle Occipital Gyrus		39	-81	12	222	10.2
	BA 18 (V3A)	30	-87	-3	15	8.4
L Middle Occipital Gyrus	BA 19 (MT+)	-42	-75	8	94	9.8
	BA 19 (V3A)	-33	-81	12	94	7.3
		-27	-75	27	56	9.5
R Cuneus	(V3A)	18	-87	15	5	8.2
L Cuneus	(V3A)	-18	-84	21	56	9.5
R Precuneus	BA 31	30	-81	33	18	8.7
L Precuneus	BA 19 (V8/LOS)	-33	-75	-6	7	7.6
R Inferior Parietal Lobule	BA 40	42	-36	48	3	8

Voxel coordinates show the local maximum of an activated voxel cluster; BA = Brodmann Area; fR = functional region; T = T-value at voxel level.

Table 1B

Anatomical Area	Ipsilateral Stimulus in Right Visual Hemifield vs. Rest in Right Visual Hemifield						Ipsilateral Stimulus in Left Visual Hemifield vs. Rest in Left Visual Hemifield					
	BA –Area/fR	Voxel coord.			Cluster	T-Value	BA –Area/fR	Voxel coord.			Cluster	T-Value
		X	Y	Z				X	Y	Z		
R Middle Temporal Gyrus	BA 37 (MT+)	54	-69	0	25	8.7	BA 37 (MT+)	48	-69	3	56	11.4
	BA39 (MT+)	48	-60	6	25	8.2						
L Middle Temporal Gyrus							BA 37 (MT+)	-42	-69	3	3	7.6
R Middle Occipital Gyrus												
L Middle Occipital Gyrus	BA 19 (MT+)	-51	-72	3	34	9.5						
R Cuneus							BA 18 (V1/V2)	18	-93	15	40	10.4
L Cuneus	BA 18 (V1/V2)	-9	-96	6	196	11.4	BA7	24	-81	30	2	7.7
R Precuneus												
L Precuneus												
R Inferior Parietal Lobule												
L Lingual Gyrus	BA 18 (V1/V2)	-21	-78	-15	196	10.3						
	BA 17 (V3v)	-6	-90	-3	196	9.2						

Voxel coordinates show the local maximum of an activated voxel cluster; BA = Brodmann Area; fR = functional region; T = T-value at voxel level.

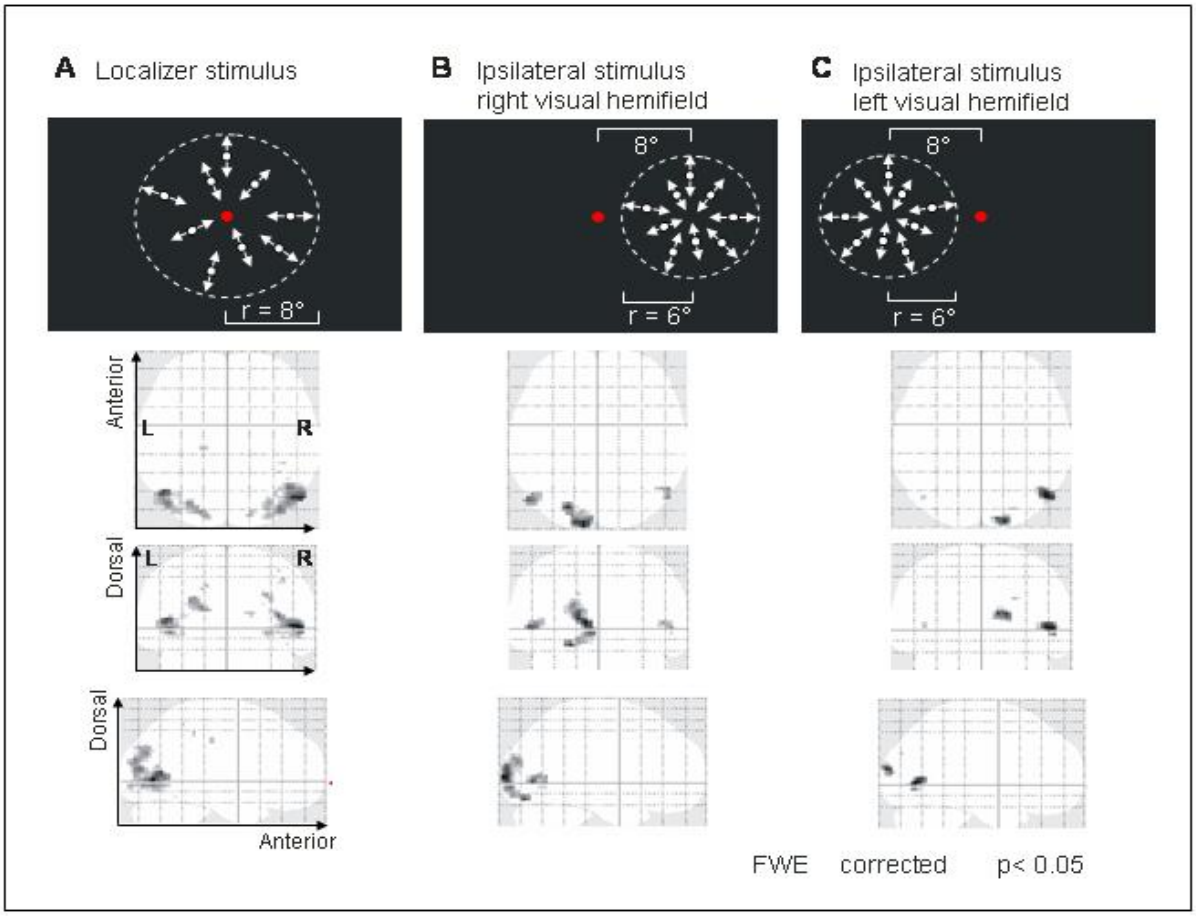

Fig. 1 Schematic drawing of stimuli and corresponding cortical activations. (A) Localizer stimulus, (B) Ipsilateral stimulus in the right visual hemifield, (C) Ipsilateral stimulus in the left visual hemifield. Contrasts calculated vs. corresponding rest conditions; FWE corrected, n=18. Glass brain presentation of data in axial, coronal and sagittal planes.

The group analysis of the ipsilateral stimulus in the right visual hemifield showed activation in the left/contralateral MT+ region and a smaller activation in the right/ipsilateral MT+ region. Furthermore, we found activation in the left/contralateral cuneus and the left lingual gyrus (table 1; Fig. 1B).

The group analysis of the ipsilateral stimulus in the left visual hemifield showed activation in the right/contralateral MT+ region and only very small activation in the left/ipsilateral MT+ region. Further significant activations were located in the right cuneus (table 1; Fig. 1C).

The above stated activations in MT+ were all located within the activated areas of the MT+ localizer stimulus (Fig. 2AB, depicted in blue). In the right hemisphere, they were clearly separated in a more anterior, ipsilateral activation (Fig. 2B red) and an adjacent, more posterior, contralateral activation in the MT+ region (Fig. 2B, green on blue). In the centre of activation the two sub areas had a small area of overlap (Fig. 2B, whitish). In the left hemisphere ipsilateral activation was similarly located in the frontal part of the MT+ region

(Fig. 2A, red – whitish), however it was not separated from the contralateral activation which spread out further to the anterior part of MT+ (Fig. 2A).

The localizer stimulus did not lead to any activation in visual areas lower than V3A, especially the primary visual cortex. Furthermore, during stimulation of the ipsilateral visual hemifield we did not find any activation outside MT+.

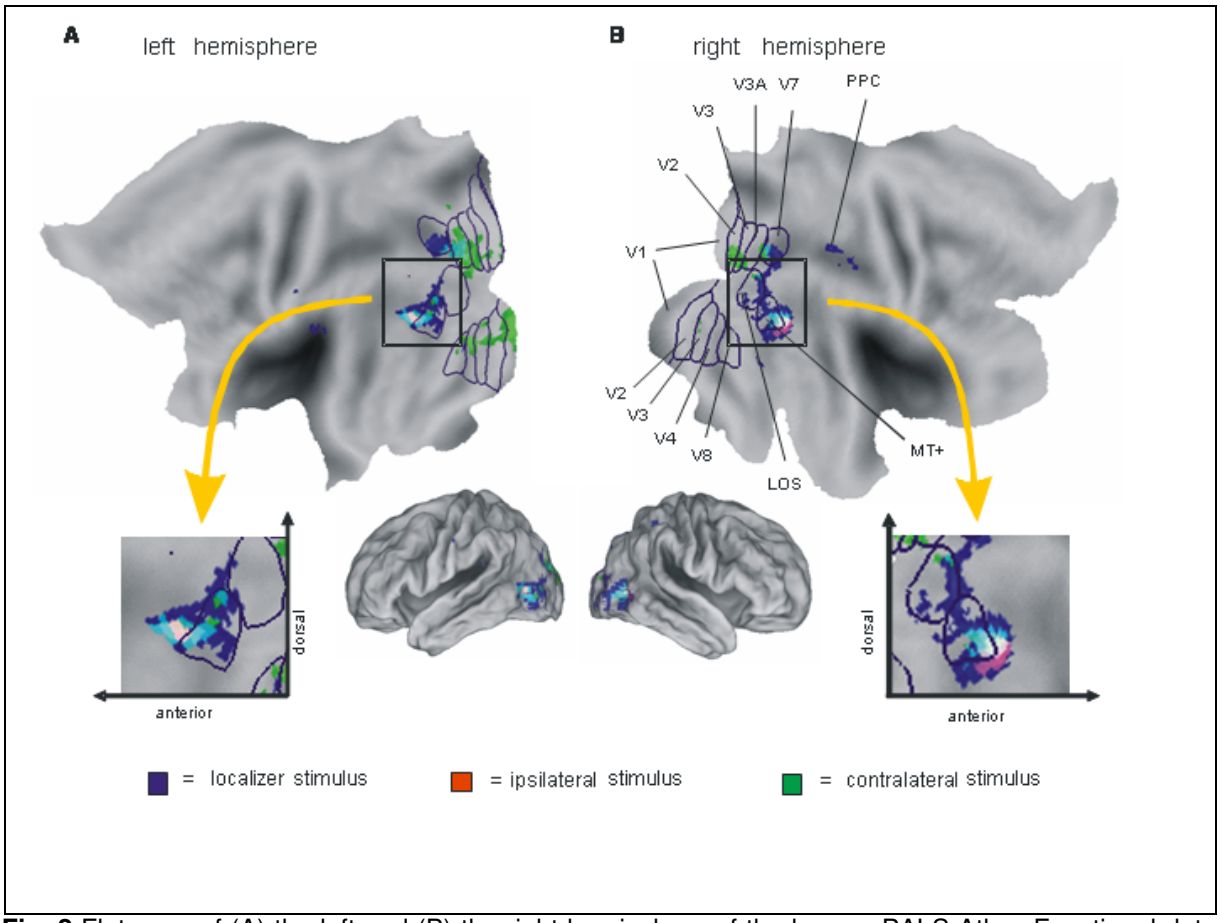

Fig. 2 Flatmaps of (A) the left and (B) the right hemisphere of the human PALS Atlas. Functional data overlaid on the flattened template brain. Functional data are RGB coded, intensity scaled to arbitrary values between 0-255. Blue, localizer stimulus activations; red, ipsilateral stimulus activations; green, contralateral stimulus activations. Mixed colors show overlay of activation. T= 6. Insets show enlarged sections of the MT+ complex. For ease of interpretation known human visual areas are outlined in blue, taken from human PALS atlas (Van Essen, 2005), and a lateral view on the slightly inflated 3D PALS template is given.

Discussion

In this experiment we investigated the human MT+ complex using optic flow stimuli located in the centre of vision (localizer stimulus) and in a circumscribed area of the right and left visual hemifield close to the midline (ipsilateral stimuli) .

Subjects performed central fixation correctly during the whole stimulation period. We localized MT+ on the ascending limb of the inferior temporal sulcus (corresponding to the junction of Brodmann areas 19, 37, 39). Comparing optic flow and static visual stimulation in the two visual hemifields we identified two subregions within the human MT+ complex on group level. One subarea was located more in the anterior part of MT+, being activated by ipsilateral and contralateral stimulation. This subarea supposably corresponds to MST. A second subarea was located in the more posterior part of MT+, and was activated exclusively by the contralateral stimulation. This subarea presumably represents MT. The location of subregions MT and MST from our group level data are in line with previous results showing single subject data [23;42;43].

While others reported great interindividual differences concerning the subregions of MT+ [44], we measured a large group of subjects, which enabled us to perform a RFX analysis. The RFX analysis largely compensates for interindividual differences. Our results of MT and MST subdivisions therefore allow for a generalization to the population level [45].

We did not only perform a region of interest analysis of the human MT+, but analyzed the whole brain. We could show that MT+ was the only region being activated by stimulation of the ipsilateral visual hemifield. Furthermore, we could show that even rather slow velocity stimuli (0.5 to 4.2°/s) led to strong activations in motion sensitive subregions MT and MST, comparable to activations obtained with velocities in the mid and high range (8°/s – 30°/s; [23;46-48]). We conclude that the interaction between the subregions MT and MST function properly across a broad range of stimulus velocities, also within this slow velocity range.

In monkeys, receptive fields of MST neurons extend far into the ipsilateral visual field (up to 40°), while the receptive fields of MT cells only extend a few degrees (up to 10° - 15°) into the ipsilateral visual field [49-53]. To avoid intermingling between MT and MST activations within the MT+ complex, some authors chose to set the edge of the ipsilateral stimulation pattern beyond the estimated distance, with which contralateral MT receptive fields might reach into the ipsilateral hemifield (about 10°-15° transferred from monkey studies; Huk et al. [54], Dukelow et al. [23]). In our approach, we placed the ipsilateral stimulus near to the center (offset of edge of stimulation pattern 2°), i.e. well within the hypothesized receptive field size of contralateral MT cells. Surprisingly, we still measured two distinct and rather

circumscribed subregions within the MT+ complex, one in the anterior part with ipsilateral stimulation, one in the posterior part with contralateral stimulation. Of course, we cannot completely rule out that our anterior activation represents a mixture of MT plus MST activations. However, the locations of our subregions resemble those of the previous studies. We therefore tend to infer that activations of contralateral MT cells, whose receptive fields reach into the ipsilateral hemifield, play a minor role in this context. Furthermore, to our knowledge, there are no data available about receptive field sizes of MT cells in humans. The unscreened assumption that MT receptive field sizes can be transferred from monkey to human might therefore require reevaluation. Note that we did not find any contralateral activation outside the MT+ complex resulting from ipsilateral stimulation.

Our localizer stimulus activated parts of V3A, V7, LOS, MT+ and the intraparietal sulcus. Surprisingly, we did not find any activations below V3A, especially V1 and V2 were not significantly activated. In contrast however, our ipsilateral stimulus did activate the contralateral visual areas V1, V2. Currently, we can only speculate about the reasons for this astonishing result. It could result from the smaller receptive field sizes in V1 at central as compared to peripheral representations. Small corrective eye movements might then lead to more activation in the central (localizer) rest condition than in the hemifield (ipsilateral) rest condition. The main contrast (central localizer stimulus – localizer rest) would therefore result in no activation in V1, while the contrast (ipsilateral stimulus – ipsilateral rest) would show activation in V1. Furthermore, V1 activation could depend more on peripheral than on central motion, or, central flow field stimulation involving both hemifields could lead to suppression of the V1 activation. Further investigations are needed to elucidate this observation. Similar activations in V1 were shown by others (for hemifield stimulation Brandt et al. [55], Nelles et al.[56]; for central flow field stimulation (localizer) Orban et al. [57]) without discussing the differences between central and hemifield flow stimulation. Goosens et al. [58] in contrary reported V1 activation resulting from a large optic flow localizer stimulus.

In conclusion, we localized two subregions of the motion processing MT+ complex on group level. One subregion is localized in the more anterior part of MT+ and activated by contralateral and ipsilateral visual hemifield stimulation. Presumably, it represents subregion MST. The second subregion, presumably MT, is localized more posterior and exclusively activated by contralateral visual hemifield stimulation. The comparison with previous studies showed that the eccentricity of the flow field relative to the mid-line plays a minor role for the location of the MT+ subregions. This result questions the assumed size of MT receptive fields in humans. The primary visual cortex did only react to our contralateral visual motion

stimuli. The particular role of the primary visual cortex in motion processing has to be elucidated in further studies.

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Chapter 5

Modulation of BOLD activations of the SPEM network as a function of the amount of background dots

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Running title: Background modulated BOLD activity in smooth pursuit eye movements

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Abstract

To perform smooth pursuit eye movements (SPEM) visual motion information has to be processed and transformed into an oculomotor output signal. In a former study (Kimmig et al. 2007 in revision) we found two regions MT+ and PPC which seemed to execute a visuo-to-oculomotor transformation (retinal to head/space coordinate transformation). Both were activated by visual as well as oculomotor stimulations.

With the help of functional magnetic resonance imaging (fMRI) and by simultaneously measuring eye movements we investigated the BOLD responses to visual, oculomotor and visuo-oculomotor stimuli. We used a parametric approach in order to explore functional differences of the possible visuo-oculomotor transformation sites and other cortical areas of the SPEM network. Human subjects had to (1) fixate a central dot, while different amounts of background dots were moving (visual stimulation), (2) pursue a central moving dot with their eyes while different amounts of background dots were moving in parallel (oculomotor stimulation) and (3) pursue a moving dot while different amounts of dots were stationary (visuo-oculomotor stimulation).

In the current study we could show that areas of the whole SPEM network can be differentially modulated by the amount of background dots depending on retinal or oculomotor information or a mixture of both. Integration of visual and oculomotor information seems to take place in MST and V7/LOP, processing of differential motion of eye and background (reference frame information) seems to take place in the PPC. Surprisingly PPC hardly reacted when eye and background moved in phase. Basal visual areas like V1 seem to receive extra-retinal (eye movement) information.

Introduction

Smooth pursuit eye movements (SPEM) help to observe moving objects in complex natural backgrounds. They have been extensively studied in monkeys using mostly electrophysiological methods (for review see Thier and Ilg 2005) and humans using psychophysical methods (Berryhill et al., 2006; Blohm et al., 2005; Collewijn and Tamminga, 1984) or cortical imaging methods like PET (O'Driscoll et al., 2000) and fMRI (Berman et al., 1999b; Kimmig et al., 2001; Lencer et al., 2005; Petit and Haxby, 1999; Rosano et al., 2002; Tanabe et al., 2002). In human cortex the frontal eye fields (FEF), supplementary eye fields (SEF), the motion sensitive middle temporal area (MT+), the posterior parietal cortex (PPC), the Cingulate Gyrus (CG) (Berman et al., 1999b; Konen et al., 2005; Lencer et al., 2005; O'Driscoll et al., 2000; Petit and Haxby, 1999; Rosano et al., 2002; Tanabe et al., 2002; for review see Krauzlis 2004) are taking part in the control of SPEM. Furthermore, parts of the thalamus (Tanaka, 2005), parts of the basal ganglia, such as the putamen (Kimmig et al., 2007 in revision), the caudate nucleus and the substantia nigra pars reticulata (SNr) participate in the control of SPEM (Cui et al., 2003).

Information of visual moving objects is transferred from the retina via optic nerve and tract to the lateral geniculate nucleus and then to the striate cortex where the stimulus is coded retinotopically. The object position has to be calculated such that the eye can be moved and centered on the object with a saccade (Blohm et al., 2005). The velocity of the object must be predicted so that the eye can pursue the object correctly and thus reduce the retinal error (Lisberger et al., 1987). For this purpose the visual input signal must be transformed to a motor command signal, which is controlled by a feedback mechanism comparing eye and target positions (Lisberger et al., 1987; Robinson et al., 1986). This motor signal operates in head /space coordinates. Thus, a coordinate transformation from retinal to head /space coordinates has to take place (visual input coded in retinal coordinates, oculomotor output coded in head/space coordinates).

It has been shown that in monkey a special part of the posterior parietal cortex (PPC), namely the ventral intraparietal cortex (VIP), is concerned with the integration of multimodal information about the external world (Andersen et al., 1998; Bremmer, 2005; Grefkes et al., 2002). Bremmer et al. (2005) showed evidence for a coordinate transformation from visual into head-centered representation in monkey VIP, but supposed that there are several other cortical areas in the visual system, which are able to perform coordinate transformations. However, the area VIP in the monkey seems to link reference frame information to the visual and head-centred position information of visual objects. Furthermore, Bremmer et al. (2005) showed that also neurons coding visual information in head-centred coordinates might carry an eye position signal. In addition the lateral intraparietal area (LIP) on the lateral wall of IPS

has been shown to participate in the planning of eye movements (Andersen et al., 1998; Snyder et al., 1997).

The motion sensitive area MT+ has equally been shown to process visual (retinal) input and eye movement signals (Bremmer et al., 1997; Ilg and Thier, 2003).

For humans it has been reported in behavioural and functional imaging studies that in analogy to the monkey the PPC, and especially the cortex within and near to the intraparietal sulcus (IPS), is crucially involved in coding object- and space-relevant information (see e. g. Corbetta et al., 2002 ; Fink et al., 1997; Vogeley and Fink, 2003). Furthermore it has been reported that the areas within the intraparietal sulcus (IPS) are multimodal areas (Bremmer et al., 2001; Grefkes et al., 2002) which code visual motion and eye movement information and subserve visuomotor transformations (Grefkes et al 2004). For the motion sensitive area MT+ it has also been shown that it processes visual (retinal) and extra-retinal (head-centric) information (Dukelow et al., 2001; Goossens et al., 2006).

In a former study (Kimmig et al., in revision) we found two regions which could perform a visuo-to-oculomotor transformation or a retinal to head/space coordinate transformation: MT+ and PPC. Both were activated by visual as well as oculomotor stimulation. While MT+ is involved in the integration of visual and oculomotor motion signals, PPC is capable of integrating polymodal signals (visual, motor, somatosensory, acoustic, effects of attention, etc.). However, a description of the functional specialization, task sharing and interaction between these two regions during smooth pursuit eye movements is lacking to date. Furthermore it cannot be excluded that also other cortical areas are able to perform these coordinate transformations (Bremmer, 2005).

In a previous study using optic flow stimuli we localized MT+ (Ohlendorf et al., submitted) and identified the MT and MST subregions on group level. Since we used exactly the same subjects and equipment as in the current study we are able to refer to the former results and the location of MT+. In the actual study we investigated the BOLD responses to visual, oculomotor and visuo-oculomotor stimuli using a parametric approach. We tested whether cortical activations are dependent on the amount of coherently moving dots, in the above mentioned three stimulus conditions and in all regions of the SP-system. In MT+ we expected an increase in activation with increasing amounts of dots in the visual motion condition. In the oculomotor conditions, we previously suggested that the eye movement signal is continuously dispersed across the visual map of MT+ (Kimmig et al., in revision). Accordingly, the cortical activation should be independent of the amount of moving dots in that condition. With this approach we intend to reveal the different functions behind the BOLD activations in the SP system.

With the help of fMRI imaging and by simultaneously measuring eye movements we investigated the cortical BOLD response of human subjects during (1) fixation of a central dot,

while different amounts of background dots were moving, (2) ocular pursuit of a central moving dot while different amounts of background dots were moving in parallel and (3) ocular pursuit of a moving dot while different amounts of dots were stationary.

Material and Methods

Visual Stimulation

Visual stimulation was performed on a PC using Matlab (R.14, The Mathworks, Natick, MA) (Fig. 1). The PC controlled a tricolour LED-board (60 x 30 cm = 23 x 12° of visual angle, 8192 LEDs) at a refresh rate of 1 KHz. The stimulation paradigm of this experiment was an extension of the one we used in (Kimmig et al. 2007, submitted). In the present study we used a retinotopically more widespread visual stimulus (ca. 20 x 10° of visual angle vs. 10 x 4° of vs. angle in the former experiment). To avoid disturbing effects of motion of the frame of reference on the retina in this experiment (similar to the former experiment) great care was taken to completely darken the room and to avoid stray light. Further, the LED-board was dimmed such that subjects in the scanner, even after dark adaptation, saw nothing except the visual stimulation dots. The LED-board was placed behind the gantry at a distance of 140 cm to the subjects' eyes.

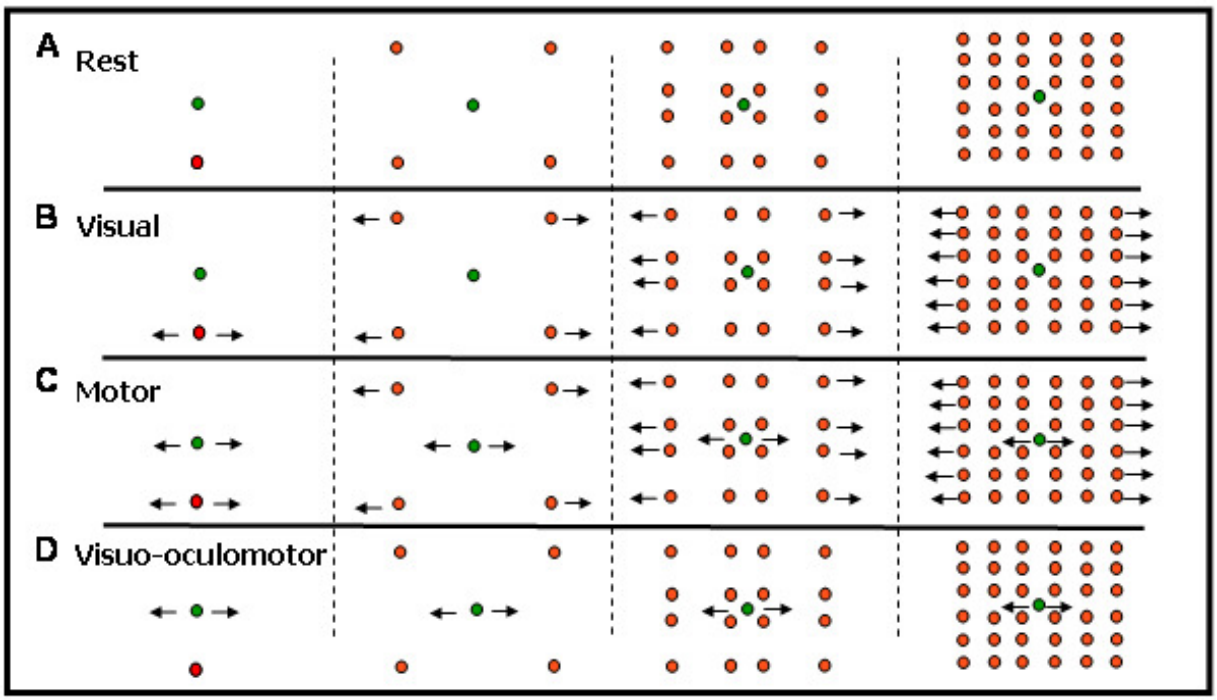

Fig. 1 Schematic drawing of visual stimulation tasks. (A) One fixation dot (green color) and 1, 4, 16 or 36 background dots (red color) are presented in complete darkness. All dots are either stationary (rest condition), or (B) the fixation dot is stationary, the 1, 4, 16, or 36 background dots move sinusoidally in the horizontal plane (visual stimulation), or (C) the green dot and all 1, 4, 16, or 36 background dots move horizontally in parallel (oculomotor stimulation), or (D) the fixation dot moves horizontally, while the 1, 4, 16, or 36 background dots remain stationary (visuo-oculomotor stimulation). Subjects had the task to always fixate or pursue the green dot.

One green fixation dot in the central screen position and, depending on the task, four different amounts of red background dots (0.1° of visual angle) could be perceived around the central screen position. The fixation dot and at least one background dot were continuously visible. During the rest periods (duration 15s) all dots remained stationary. During all conditions the subjects had to fixate or pursue the central dot (Fig. 1A). Three different stimulation types occurred in alternation with the rest periods (duration 15 s each): (condition 1) the background dots moved sinusoidally in the horizontal plane and subjects had to fixate the stationary fixation dot (resulting in pure visual stimulation due to the movement of the background dots across the retina) (Fig. 1B), (condition 2) both, the fixation dot and the background dots moved in parallel sinusoidally in the horizontal plane, subjects had to track the fixation dot with their eyes (resulting in predominantly oculomotor and only little sensory/visual stimulation due to retinal slip; for ease of use we will call this the oculomotor stimulus - knowing that the resulting eye movement is in fact a visually driven oculomotor response) (Fig. 1C), (condition 3) the fixation dot moved sinusoidally in the horizontal plane and subjects had to track this dot with their eyes, the background dots remained stationary (resulting in visual stimulation due to relative motion of the lower dot across the retina plus additional visually driven pursuit motor activity with only little retinal slip stimulation; in the following we will call this stimulus the visuo-oculomotor stimulus; Fig. 1D). Either dot moved up to an angle of ±5° at a velocity of 0.33 Hz (peak velocity 10° s^{-1}). The number of background dots of every stimulation type varied parametrically in four steps (n = 1, 4, 16 and 36 background dots) resulting in 16 different conditions (4x visual, 4x motor, 4x visuomotor, 4x rest). The twelve stimulation conditions (i) visual (1, 4, 16, 36 background dots), (ii) oculomotor (1, 4, 16, 36 background dots), (iii) visuo-oculomotor (1, 4, 16, 36 background dots) occurred in a pseudo-random fashion in alternation with the rest conditions (fixation dot plus 1, 4, 16, 36 background dots, all remaining stationary). Every stimulation condition was repeated twice, every rest condition six times. Each subject performed three series (Fig. 1B). For stimulation order see Fig. 2.

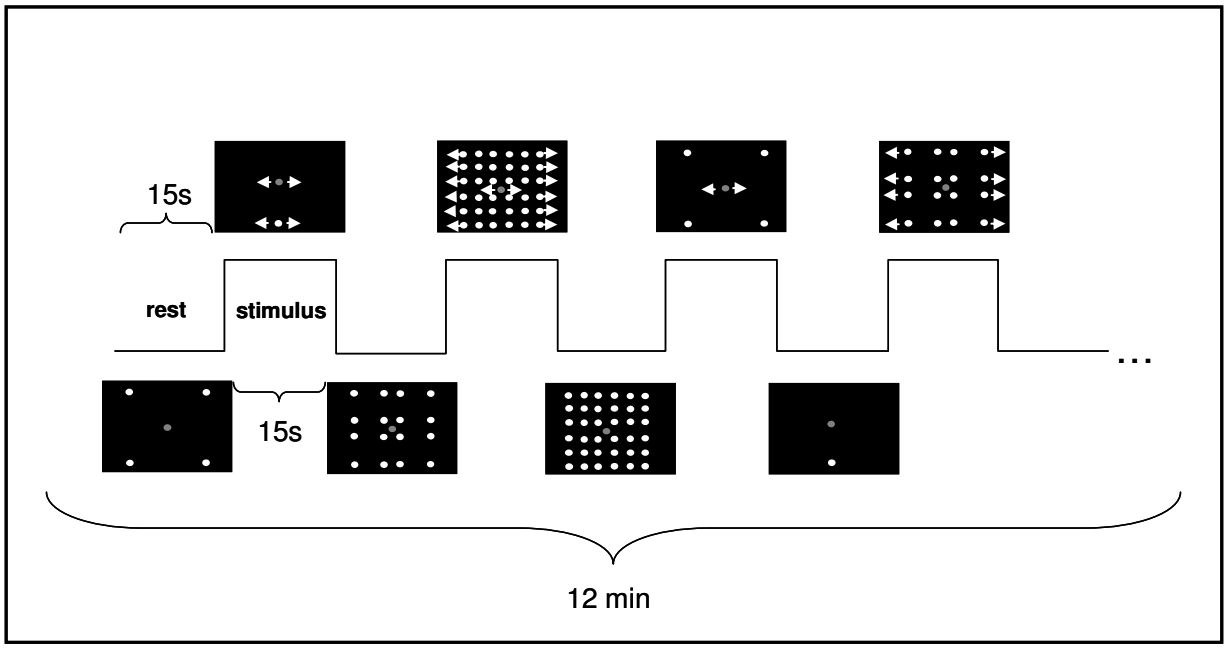

Fig. 2 Exemplary order of visual stimulation tasks (alternating stimulation and rest conditions) occurring in pseudo-randomized order.

MR Eye-tracking

For eye movement recordings we used the Freiburg MR-Eyetracker system, a fibre-optic limbus tracking device (Kimmig et al., 1999). A multi-channel computer program (LabVIEW, National Instruments, Austin, Texas, USA) was used to acquire and display the signals derived from the MR-Eyetracker. The sampling frequency was 500 Hz; the best spatial resolution was 0.2° of visual angle. The stimulus position was displayed and recorded in parallel to the eye movement data. The MR-scanner provided a TTL-pulse at the beginning of each volume acquisition. This pulse was used to trigger both our stimulation and the eye movement acquisition programs. The eye movement data was calibrated to a reference stimulus signal (±5° of visual angle).

MR-Imaging

Magnetic resonance imaging was performed with a 3 Tesla Magnetom TRIO research scanner (Siemens, Erlangen, Germany). The scanner was equipped with a standard 8-channel send-receive circularly polarized headcoil (CP-Headcoil). Functional imaging was performed with a T2*-weighted gradient recalled echo-planar imaging (EPI) sequence which was performing a fully automated motion and distortion correction during image reconstruction (Zaitsev et al., 2004). High-resolution, sagittal T1-weighted images were acquired with the MP-RAGE (magnetization prepared rapid acquisition gradient echo) sequence to obtain a 3D anatomical scan of the brain. Shimming was performed for the entire brain using an auto-shim routine for

magnetic field homogeneity. The technical parameters of the fMRI sequence were TE 30 ms, TR 2.5 s, flip angle 90°, matrix 64 x 70 and a voxel size of 3 x 3 x 3 mm^3.
The stimulation protocol for each stimulation sequence of the experiment consisted of forty-eight 15 s intervals including 24 periods of rest (OFF) and 24 periods of stimulation (ON) in alternating order. This protocol produced 288 echo planar volumes per series (duration 12 min). Each subject performed three series.
Data acquisition was performed in 36 slices per volume containing the whole brain except for ventral parts of the cerebellum. To minimize head motion, the subject's head was fixed in the MR headcoil. The effects of the gradient noises were reduced by sound-dampening headphones.

Subjects

Twenty healthy subjects took part in this study. Two subjects were excluded from analysis because of fatigue resulting in 17 right handed and one left handed subjects which were the same as in Ohlendorf et al. (submitted). Age ranged between 18–35 years, vision was normal or corrected to normal. Written informed consent was obtained from all subjects. The study was approved by the Ethics Committee of the University of Freiburg, in accordance with the Declaration of Helsinki.

Eye movement data analysis

Previously we showed, how saccades influence the cortical BOLD activation (Haller et al., 2007; Kimmig et al., 2001). Therefore, eye movement data were analyzed separately for smooth pursuit eye movements and contaminating saccades were detected by an interactive computer program. Saccade detection was performed by a velocity threshold algorithm (velocity threshold 35°/s). The algorithm detected saccades greater than 0.35°. Saccades smaller than 0.35° were determined interactively. Saccade detection below the noise level of 0.2° was not performed. We calculated the mean saccade amplitude per time interval and counted the number of saccades per fixation and stimulation period, respectively (saccadic frequency). Since saccades in the pursuit signal are to some degree inevitable, the measures of saccadic frequency and mean saccade amplitude indicate whether saccades are balanced between rest and stimulation periods. Artifacts like drifts or blinks were identified visually and removed.
Pursuit eye position was filtered by a median filter (15 samples) and a 100Hz Gauss Filter and differentiated to yield eye velocity. After extraction of saccades, drifts and blinks from the pursuit velocity trace, the remaining pursuit data were interpolated linearly. The sinusoidal eye velocity signal was calculated using an eight samples differentiation calculation i.e. subtracting the mean of the following eight samples from mean of the previous eight samples. The eye

velocity signal was then fitted by a Marquardt-Levenberg method (Borse, 1997) using five cycles of smooth pursuit. As a measure for the goodness of SP performance we used the velocity gain. The gain was defined by the ratio of eye velocity to target velocity (a gain of 1 represents optimal pursuit).

FMRI data analysis

We used the software package SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Since residual head motion could have stayed over in some of the image data despite head fixation in the scanner head coil and automated motion correction, the first preprocessing step of the functional MRI data consisted in motion correction via SPM5 realignment. Then, for multiple comparisons, we normalized the EPI images by segmentation of the T1 image and using resulting segmentation parameters to write the normalized EPI volumes. The last preprocessing step consisted in spatial smoothing with Gaussian spatial kernels of 8 mm (full width at half maximum).

For statistical analysis the data was fitted to a general linear model to establish parameter estimates for each subject. Contrasts were defined to yield the sizes of the main effects of (1) the four rest conditions (rest-condition including 1, 4, 16, 36 background dots) (2) the four visual stimulations (visual stimulation including 1, 4, 16, 36 background dots), (3) the four oculomotor stimulations (oculomotor stimulation including 1, 4, 16, 36 background dots and (4) the four visuo-oculomotor stimulations (visuo-oculomotor stimulation including 1, 4, 16, 36 background dots) in every subject. In order to avoid contaminating activation due to correction saccades during the different conditions we modulated parametrically for saccadic frequency on the single subject level. With this method we discarded BOLD responses due to frequency of correction saccades from our calculated contrasts.

Group level statistic was performed by including the individual contrast images for the sixteen main effects of 18 subjects into a second level random effects Flexible Factorial Design analysis. The specific effects were tested with appropriate T-contrasts and corrected for multiple comparisons (family wise error correction (FWE)). Clusters of voxel surpassing an individual threshold of $p = 0.05$ (corrected) were considered as significant activations.

We calculated differential contrasts of the twelve stimulation tasks vs. the equivalent rest condition (e.g. visual condition with 4 background dots – rest condition with 4 background dots).

Furthermore, we calculated contrasts of the three different main stimulation types performing linearly increasing parametric modulation of the amount of background dots in order to see which areas increase linearly in relation with the different stimulation types.

For visualization purposes we projected the functional group results onto the left and right hemispheres of the Human Colin surface-based atlas mapped to PALS ('Population-Average Landmark- and Surface-based'-atlas; Van Essen, 2002; Van Essen, 2004; Van Essen, 2005). This atlas is derived from structural MRI volumes of 12 normal young adults. Data were mapped on the flatmap template and the three dimensional cortical template of the atlas. This was done using the Computerized Anatomical Reconstruction and Editing Toolkit (CARET) version 5.3 (http://brainvis.wustl.edu; Van Essen et al. 2001). Grid dimensions for conversion of analyzed volumes to CARET metric files were set to the SPM default values.

Statistical representations of the grey matter activations of the three main effects were mapped to different colours in functional overlays. Co-activated regions are displayed by weighted additive colour while pure colours indicate regions activated by only one of the tasks (visual – red; oculomotor – blue; visuo-oculomotor – green; intensity scale 0 – 255 referring to the maximum activation of each contrast). Please note that in this view we show only grey matter activation locations. Activations located in the white matter which are visible in the SPM glass brains cannot be seen here. Furthermore, the flatmaps show exclusively activation locations and their overlaps surpassing a given T-threshold. In the flatmaps we used a lower T-threshold of T = 3.5 (correspond to uncorrected data activations). With this uncorrected threshold we wanted to show that non-activation of certain areas of the SPEM network during some of the tasks is not only due to the very rigid FWE correction threshold used in the SPM glass brains. Note that in the flatmaps we see activation maxima without considering differences of effect sizes in the given conditions/tasks.

We report all findings in the MNI (Montreal Neurological Institute) coordinate system. Activation localization was performed via the SPM5 tool 'wfu pickatlas' (Maldjian et al., 2003; Maldjian et al., 2004). We consider only forebrain activations; cerebellar and brainstem activations were not included in the statistical analysis.

Results

Eye movement data

Subjects followed the moving dot accurately in both pursuit condition types. SPEM gain was close to unity in both tasks (mean gain oculomotor task 0.94, mean gain visuo-oculomotor-task 0.87) (Fig. 3 A). The gain was lower in the visuo-oculomotor-condition than in the motor condition. Saccades occurred at significantly lower frequencies (Fig. 3B) and amplitudes (Fig. 2C) during rest and visual stimulation periods than during pursuit periods. In all conditions amplitudes of correction saccades were quite small (max. 1.1° of vis. angle). The oculomotor data were used to modulate parametrically the BOLD responses on the single subject level. With this method we avoided a contamination of the SPM contrasts with saccadic activation.

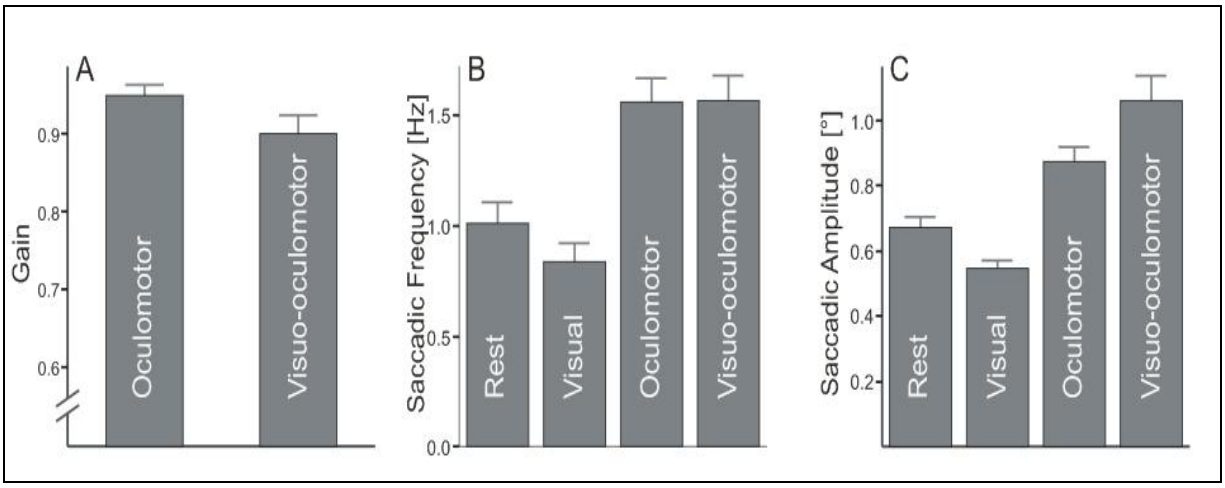

Fig. 3 Eye movement data of the four stimulation types. (A) shows the gain of the two eye movement tasks, paired T-Test, effect 'SP task' p=0.004 (B) shows the saccadic frequency of the stimulation types. Repeated Measures ANOVA, effect 'task': F=23.9; df=3; p = 0.00) (C) shows the saccadic amplitude of the saccadic amplitude. Repeated Measures ANOVA, effect 'task': F=32.391; df=3; p = 0.00 Error bars = ± 1 SE.

FMRI data

The overall visual stimulation design (stimulation type – rest) led to activations in the well known SPEM network, SEF, FEF, MT+, PPC, pCG (Table 1) and was in agreement with our former study (Kimmig et al., in revision). In the current experiment we saw more extended activations in basal visual areas V1, V2 and V3 in the visual and visuo-oculomotor tasks.

Visual stimulation vs. rest led to bilateral activations in MT+, basal visual areas (V1-V3), V7/LOP and the PPC (Fig. 4 A). Even if visual activations of only one background dot did not surpass the FWE correction (for reasons of completeness contrast shown at uncorrected T-threshold), it could be seen that activations increased when the number of moving dos increased from 1 to 16 or from 4 to 16 (Fig. 4A, column 1-4). For 36 background dots the amount of activated voxels decreased again slightly in most areas. However, in small parts of MT+, V7/ LOP, PPC and basal visual areas (V1/V2), not differentiable within activation blobs

in the mean contrasts, activation apparently increased even more for 36 background dots. This fact will be addressed in the parametric contrasts (see below). Interestingly the amount of visual activation of MT+ for 4 and 16 background dots was higher compared to the oculomotor and visuo-oculomotor stimulation.

Oculomotor stimulation led to activations in MT+, V7/LOP, FEF, pCG and basal visual areas (Fig. 4 B). Most of the activation could be seen in the one background dot condition and in the 36 background dot condition. E.g. parts of the FEF were only activated with 1 and 36 background dots (Fig. 4 B column 1 and 4). The most stable activation (in nearly all moving dot conditions) could be seen in MT+ and the pCG. We could not find any PPC-activation during oculomotor stimulation.

Visuo-oculomotor stimulation, similar to the oculomotor condition, led to activations in SEF, FEF, MT+, basal visual areas (V1-V3), V7/ LOP, PPC, pCG and addition the putamen as a part of the basal ganglia (Fig. 4 C).These activations were stronger than those of the oculomotor stimulation. In this condition type most activations could be seen in the condition with 16 background dots. All activations increased from 1 - 16 or 4 - 16 background dots. However, only MT+ and FEF activations already surpassed the FWE correction threshold in the one background dot condition. The other cortical areas of the SPEM network surpassed the threshold with four or more background dots. For 36 background dots the amount of activated voxels decreased again slightly in nearly all activated areas except in V1 and in small parts of PPC where activations continued to increase (parametric contrast see below). Activations of the putamen were only significant for 16 background dots; however, these activations are not visible in the transversal view of Fig. 4.

Anatomical Area	VisualStimulation_ vs. Rest						Motor Stimulation vs. Rest						Visuo-Oculomotor Stimulation vs. Rest					
	BA –Area	Voxel coord.			Cluster	T-Value	BA –Area	Voxel coord.			Cluster	T-Value	BA –Area	Voxel coord.			Cluster	T-Value
		X	Y	Z				X	Y	Z				X	Y	Z		
R Medial Frontal Gyrus							BA6	12	-3	66	148	6.7	BA6	-6	-6	63	847	10.3
L Medial Frontal Gyrus							BA6	-6	-3	60	148	7.8						
R Middle Frontal Gyrus	BA6	24	-6	48	15	5.2												
L Middle Frontal Gyrus	BA6	-27	-9	48	20	5.4												
R Inferior Frontal Gyrus							BA9	57	6	39	256	8.7	BA45	63	9	21	370	6.8
							BA44	60	9	18	256	5.2						
R Precentral Gyrus							BA6	48	-3	54	256	10	BA6	48	-3	54	370	12.3
L Precentral Gyrus							BA6	-57	0	39	233	8.5	BA6	-42	-9	48	847	12.2
							BA6	-42	-9	48	233	8.3	BA6	-54	0	39	847	11
R Postcentral Gyrus							BA6	30	-36	48	117	7.2		30	-36	45	165	8
L Postcentral Gyrus		30	-36	45	368	9.2												
R Superior Parietal lobule	BA 7	24	-54	57	368	9.5												
R Precuneus							BA19	24	-75	33	853	10.3	BA7	21	-57	54	165	7.9
							BA7	21	-60	51	117	6						
L Precuneus							BA7	-27	-51	51	65	6.4	BA7	-24	-57	54	258	10
R Cuneus		27	-81	27	1126	12.5												
L Cuneus		-24	-81	27	1744	12.9		-21	-78	27	281	8.9	BA18	-18	-87	18	1689	12.8
		-21	-87	21	1744	12.3		-21	84	21	281	8.7		-21	-78	27	1689	
R Middle Temporal Gyrus		45	-60	3	1126	14.4	BA39	48	-60	3	853	14.1	BA37	48	-60	3	305	15
L Middle Temporal Gyrus	BA37	-45	-69	3	1744	14.3	BA37	-45	-72	6	266	11.0	BA37	-45	-72	6	264	13.2
R Middle Occipital Gyrus		30	-81	3	1126	5.9												
R Superior Temporal Gyrus							BA22	63	-33	15	130	8.25	BA22	63	-33	15	112	9
R Putamen														21	3	9	30	6.2
L Putamen														-21	6	6	40	6.3
R Cingulate Gyrus							BA24	15	-21	45	25	7.44	BA24	15	-21	45	29	7.5
L Cingulate Gyrus							BA24	-12	-21	42	40	11.09	BA24	-12	-21	42	68	13.5
R Lingual Gyrus	BA18	12	-75	-6	76	6.8												
R Insula								39	-30	21	130	6.45		39	-30	21	112	5.3
L Insula								-42	-33	21	23	7.16		-42	-33	21	74	8.1

Table 1 Coordinates show the local maximum of an activated voxel cluster in MNI space; BA = Brodmann Area; fR = functional region; T = T-value at voxel level.

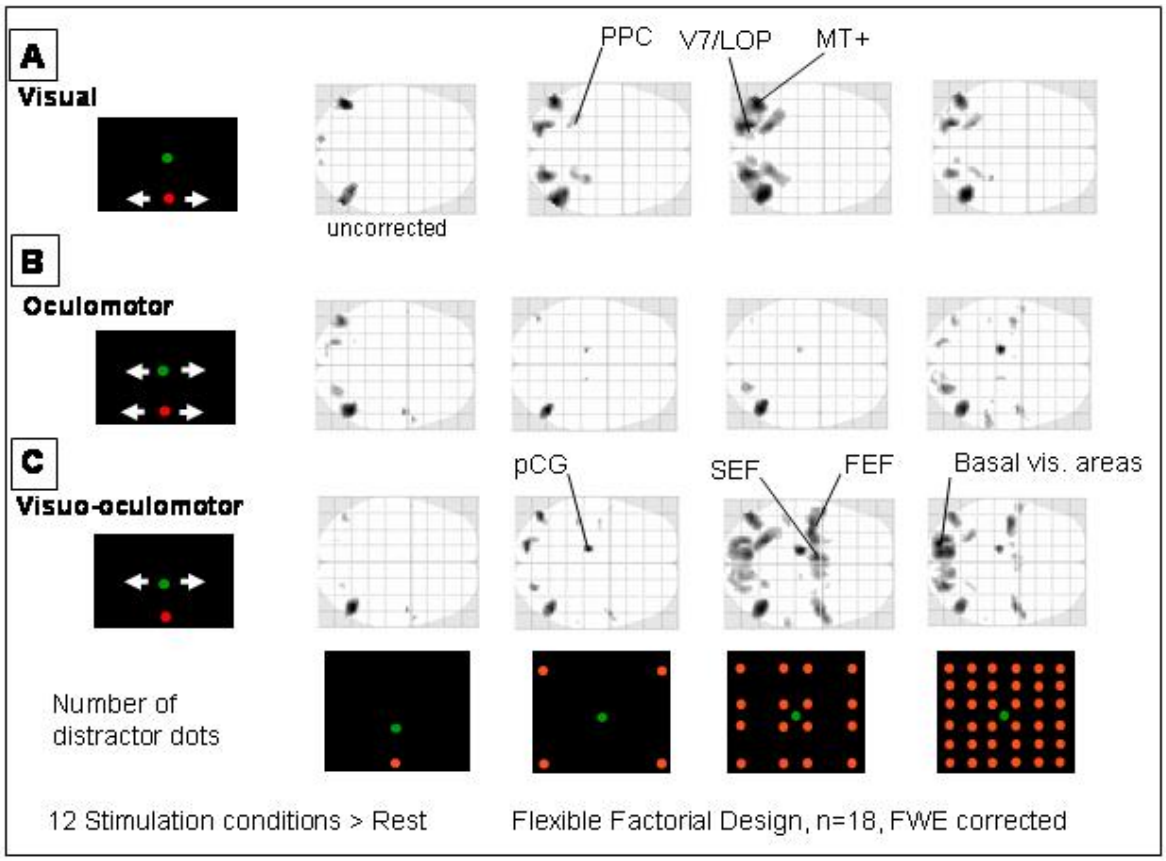

Fig. 4 Main contrasts. Cortical activation related to (A) Visual stimulation vs. corresponding rest condition, (B) Oculomotor stimulation vs. corresponding rest condition, (C) Visuo-oculomotor stimulation vs. corresponding rest condition. First column, 1 background dot, second column 2 background dots, third column 16 background dots, fourth column 36 background dots.

Parametric modulations of the amount of moving dots

In a parametric modulation of the amount of moving dots (Fig. 5; table 2) we found that during visual stimulation the activation of basal visual areas (ventral part of V1), Precuneus, Cuneus, PPC increased significantly ($p = 0.01$ uncorrected t-threshold; Fig. 5 A). Excluding the visual stimulation with 36 background dots, the amount of voxels representing a parametrical increase of activation became a lot higher and included also area V7/ LOP and MT+ (Fig. 5 B). These results statistically confirm the effects found in the SPM glass brains (Fig. 4) showing that activations mostly increased linearly up to an amount of 16 background dots and then decreased again in the case of 36 background dots.

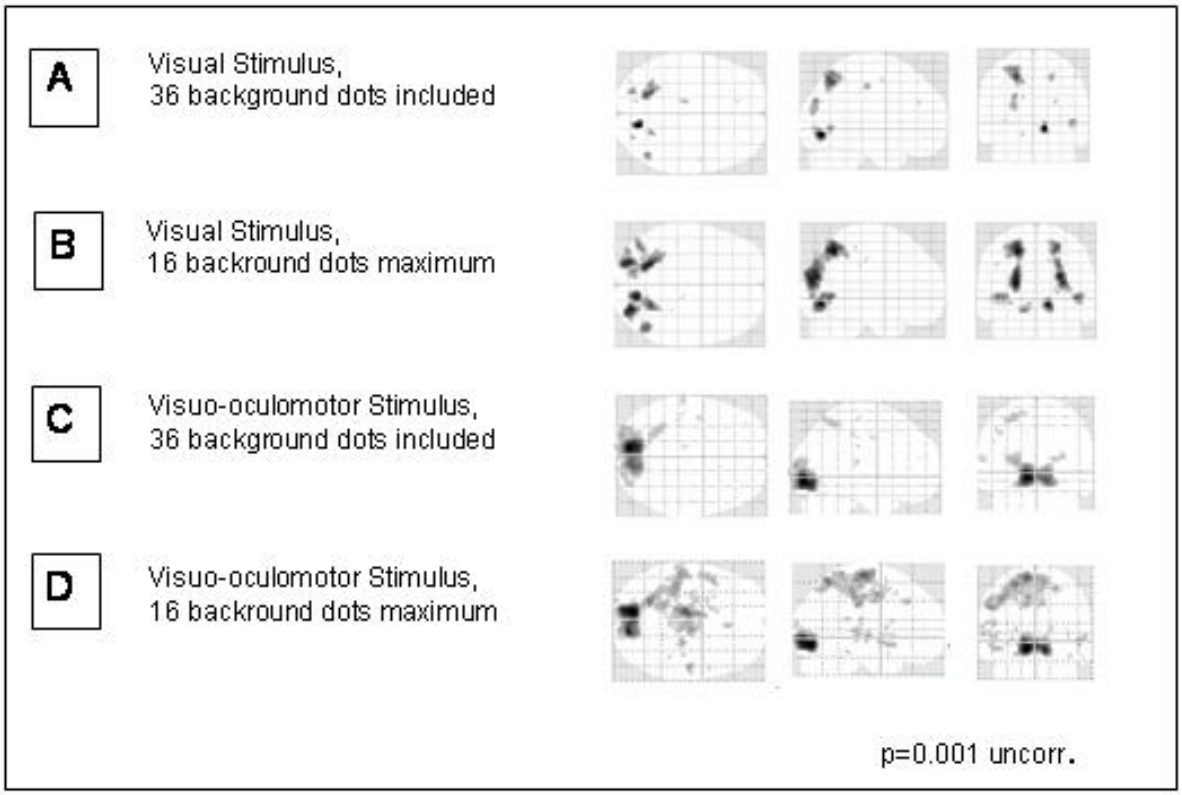

Fig. 5 Linearly increasing parametric modulation of background dots.

The parametric modulation of the oculomotor stimulation did neither show a significant linear increase nor a U-shaped function of activation effect size in dependence of the amount of background dots (contrast not shown).

Linear parametric modulation contrasts of the visuo-oculomotor stimulation showed mostly V1 activation and small PPC activation which apparently increased in correlation with the amount of background dots (Fig. 5 C). Excluding the 36 background dots condition from the parametric contrast we saw an increase of activated clusters in the PPC and in frontal areas (Fig. 5 D; see also table 2).

Taken together, these parametric contrasts confirm the results described in the glass brains (Fig. 4).

Table 2

Anatomical Area	Parametric Modulation visual stimulus (1-36 background dots)						Parametric Modulation visual stimulus 1-16 (1-16 background dots)						Parametric Modulation visuo-oculomotor (1-36 background dots)						Parametric Modulation visuo- (1-16 background dots)					
	BA –Area	Voxel coord.			Cluster	T-Value	BA –Area	Voxel coord.			Cluster	T-Value	BA –Area	Voxel coord.			Cluster	T-Value	BA –Area	Voxel coord.			Cluster	T-Value
		X	Y	Z				X	Y	Z				X	Y	Z				X	Y	Z		
L Superior Frontal Gyrus																			BA6	-9	-18	69	976	4,8
R Middle Frontal Gyrus																			BA6	9	-12	66	976	4,3
																			BA6	24	-18	57	21	3,8
L Inferior Frontal Gyrus																			BA45	-48	15	18	6	3,6
L Postcentral Gyrus																			BA40	-60	-21	16	52	3,4
R Superior Parietal lobule																			BA7	-21	-60	63	976	4,8
L Superior Parietal lobule	BA 7	-33	-60	60	138	3,7	BA7	-33	-51	57	215	3,7	BA7	-27	-51	60	59	3,8						
R Precuneus	BA7	21	-60	51				27	-78	24	189	4,9												
							BA7	21	-57	54	105	4,2												
L Precuneus		-21	-60	51	138	4,2	BA7	-21	-60	51	215	4,9												
	BA 7	-27	-51	54	138	3,6	BA31	-21	-78	30	183	4,4												
	BA19	-21	-78	33	34	3,6																		
R Cuneus								24	-81	6	189	3,4												
L Cuneus		-24	-81	18	34	3,5	BA18	-21	-84	18	183	4,7												
R Middle Temporal Gyrus	BA37	45	-63	0	18	3,8	BA37	45	-63	0	49	4,1												
L Middle Temporal Gyrus																								
R Middle Occipital Gyrus																								
L Middle Occipital Gyrus							BA19	-42	-72	3	62	3,9												
							BA19	-33	-84	3	19	3,7												
R Superior Temporal Gyrus																			BA22	51	-15	-3	23	3,9
L Superior Temporal Gyrus																			BA22	-60	-27	6	52	3,6
L Cingulate Gyrus		-12	-21	48	6	3,6																		
R Lingual Gyrus		12	-72	-3	39	4,7	BA18	15	-75	-6	77	4,7	BA18	12	-81	-9	903	5,7	BA18	12	-81	-9	566	5,6
L Lingual Gyrus								-27	-66	-3	62	3,6	BA18	-9	-84	-6	903	7,2	BA18	-9	-75	-9	566	5,9
							BA18	-12	-78	-12	46	3,8												
R Insula																			BA13	39	-21	3	5	3
L Insula																			BA13	-48	-36	21	7	3,4

Coordinates show the local maximum of an activated voxel cluster in MNI space; BA = Brodmann Area; fR = functional region; T = T-value at voxel level.

Overall activations depending on the amount of background dots

For the localization of cortical regions where activations of the different task types overlap and to find out more about multimodal regions (regions where visuo-oculomotor transformations could take place) and activation behavior of basal visual areas statistical activation results of all three stimulation types (visual (depicted in red), motor (blue), visuo-oculomotor (green)) were overlaid on cortical flatmaps (T = 3.5; methods described above; Fig. 6 A-D). An overlay of activations resulting from the two SPEM task types could be seen in frontal areas SEF, FEF and the pCG (green and blue color and mixture of those). Small activation overlap of the visual and visuo-oculomotor activations (green and red color and mixture of those) could be seen in the PPC. Oculomotor activations of the PPC existed exclusively with one and 36 background dots at this low threshold (not at FWE corr. threshold Fig. 4) Activation overlays of all three stimulation types were located mainly in MT+ and in V7/LOP, but also in basal visual areas. Basal visual areas were not significantly activated in the case of 1 and 4 background dots even at the uncorrected threshold of T = 3.5, but in contrast to the other cortical regions of the SPEM system, there, activation continued to increase with the amount of background dots up to the amount of 36 (in the oculomotor condition the tendency was not significant in the parametric contrast (Fig. 5) but visible).

As stated in the methods section for the flatmaps we used a t-threshold of T = 3.5 since we wanted to make sure that a lack of activation of PPC during oculomotor stimulation and non-existing activations in the basal visual areas are not an effect of the rigid FWE correction T-threshold.

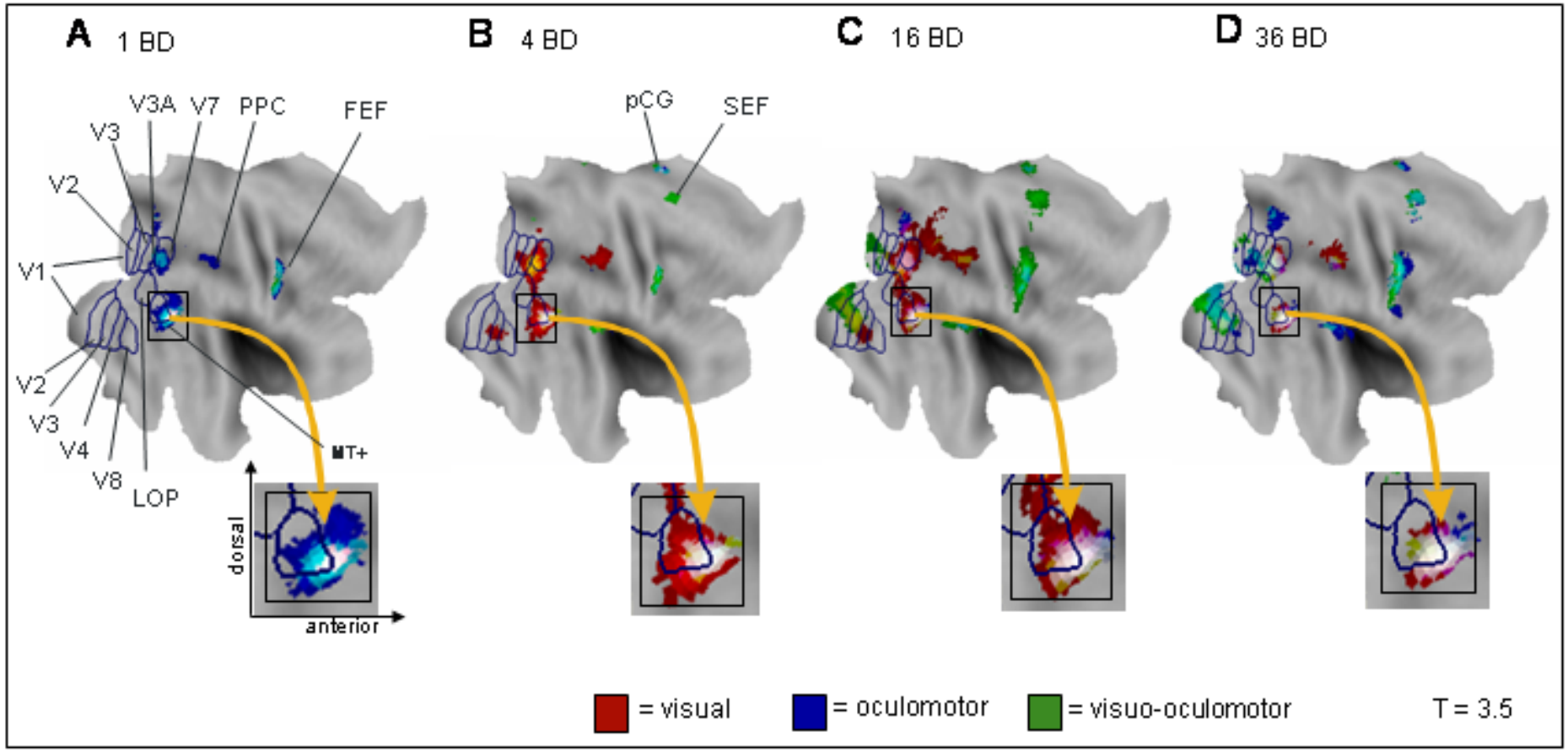

Fig. 6 SPM group activation results overlaid on flatmaps of the right cortical hemispere (PALS atlas): (A) 1 background dot (BD); (B) 4 background dots; (C) 16 background dots; (D) 36: background dots; red = visual; blue = oculomotor; green = visuo-oculomotor activation; colour mixtures = activation overlays; e.g. white = overlay of all three stimulation activations; MT+, Cuneus (V7), PPC, FEF are already activated during tasks with 1 background dot, further areas of SPEM network get only activated during motion of more than one background dot; basal visual areas (V1, V2) are not activated during stimulation with 1 and 4 background dots. Small inserts: activation of MT+ starts at frontal pole, propagating in posterior and dorsal direction for 4 and 16 background dots, refocusing anteriorly for 36 background dots.

MT+ complex: In the sections showing area MT+ (Fig. 6 arrowheads) we could see that (i) stimulation with only one background dot started at the anterior pole of the MT+ complex and that (ii) activation resulting from 4 and 16 background dots propagated in posterior and dorsal directions. Then, activation refocused anteriorly for 36 background dots, where an overlay of all three stimulation types of more or less similar size could be observed.

This anterior part of MT+ appears to be activated by retinal and extra-retinal signals and therefore presumably represents MST. To support this notion, we compared the MT+ activations obtained from overall stimulation types (all background dots amounts pooled) with the results of a MT+ subregion analysis based on the visual properties of MT+ (Ohlendorf et al., submitted). Note, that this previous study was performed with exactly the same subject group and laboratory setup. We proved that the ventral anterior part of the MT+ complex is activated not only by retinal and extra-retinal stimuli but also by contralateral and ipsilateral motion stimuli; hence it represents the subregion MST. An overlay of activations of both studies is given in Fig. 7.

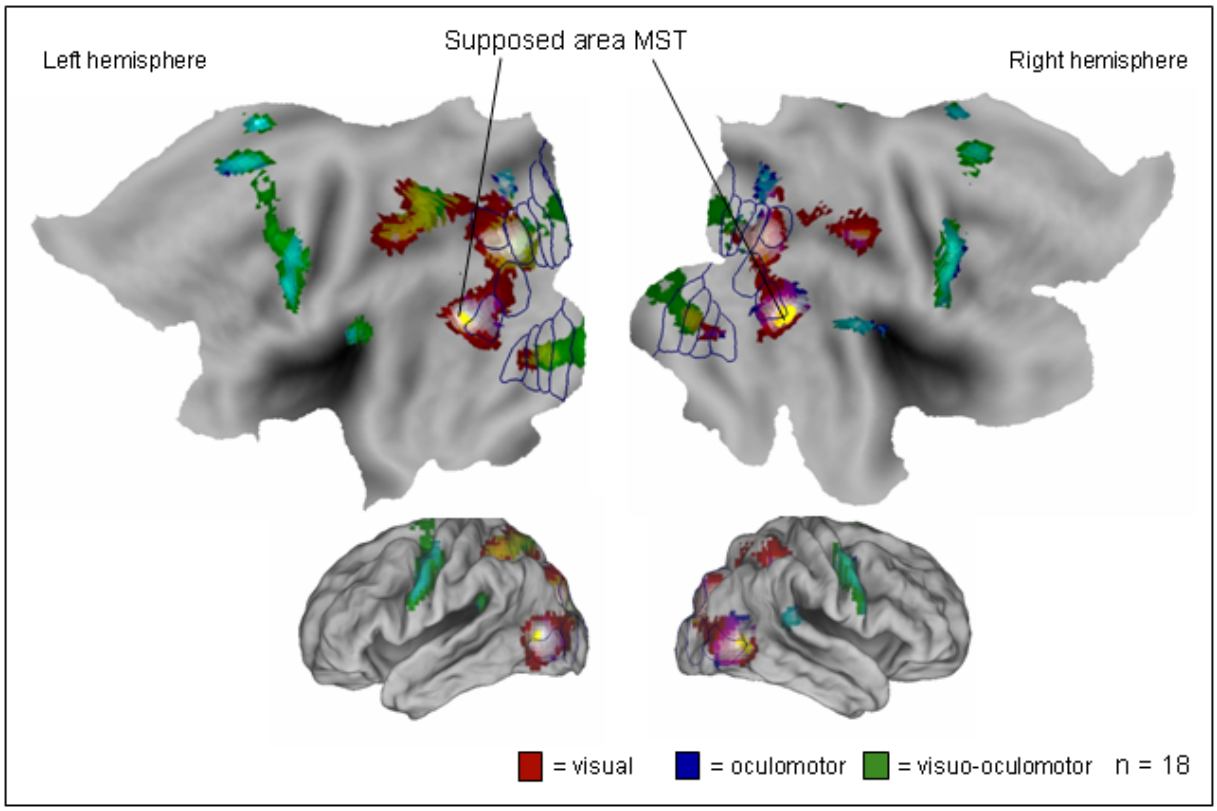

Fig. 7 Overlay of activation results of our previous study (Ohlendorf et al. 2007 submitted) in yellow colour on the cortical activation results of overall stimulation types (all background dots amounts pooled) (FWE corrected).

Discussion

To our knowledge this is the first study to measure fMRI brain activations of motion and pursuit stimuli as a function of the amount of visual dots which (i) moved coherently while subjects fixated a stationary dot, (ii) moved coherently while subjects pursued a dot moving in phase, (iii) remained stationary while subjects pursued a single moving dot. These three tasks correspond to visual, oculomotor and mixed visuo-oculomotor stimuli. Presentation of the stimuli in complete darkness avoided contamination of brain activations with SPEM induced retinal slip.

In general, visual stimulation (stimulation types 1-36 background dots) led to parieto-occipital activations located in the motion sensitive MT+ complex, V7/LOP and in the PPC. Oculomotor and visuo-oculomotor stimulation led to additional frontal activations in SEF, FEF, pCG and to basal ganglia (putamen) activation in the visuo-oculomotor task. We thereby confirmed the results of our previous study (Kimmig et al. 2007). Areas of the whole SPEM network showed to be modulated by the amount of background dots. However, these modulations where strongly depending on the stimulation type and varied across the different regions of the SPEM network. In the visual stimulation activations increased from 1-16 background dots in all visually activated regions. In contrast, in the oculomotor task activations remained more constant. In the visuo-oculomotor stimulation activations in basal visual areas PPC and frontal areas increased parametrically from 1-16 background dots. This activation increase, however, was a lot weaker than in the visual stimulation task. For 36 background dots activation in the visual and in the visuo-oculomotor stimulations did not increase anymore; in contrast, activations were slightly reduced again. Basal visual areas were only activated by stronger/larger visual stimulation (16 and more background dots). In contrast to other cortical areas, there, activation increased from 16 to 36 background dots, especially during the eye movement conditions. Possible visuo-oculomotor transformation sites were found in V7/LOP and in a subregion of MT+, supposedly subarea MST. PPC was mainly active when motion of the visual background and motion of the eye differed.

Visual processing

During visual stimulation with parametric modulation of moving background dots the shown increase of activation resulted from an increase of basal (retinal) stimulation. SEF, FEF and pCG did not participate in the processing of the visual input, even with higher amounts of background dots. Since the basic elements of the cortical motion processing stream in primates are V1 direction selective neurons (Dow, 1974; Hubel and Wiesel, 1968) in our

previous experiment we were surprised that motion of one visual dot (compared to two stationary dots) did not activate basal visual areas (Kimmig et al., in revision). However, e.g. Van Oostende et al. (1997) also described that presenting small visual stimuli motion responses were small or insignificant. Using more than one background dot in the current study showed that basal visual areas also participated in processing of visual motion input; they however needed stronger (larger) visual stimulation (16-36 background dots) to be activated significantly. This result indicates that basal visual areas seem to be less sensitive to visual motion than e.g. MT+. Furthermore it confirms indirectly that there must exist a second pathway from the retina leading to MT+ perhaps via the SC (Weiskrantz, 1996) or a direct LGN input to MT (Sincich et al., 2004; Stepniewska et al., 1999) without significant involvement of V1.

Oculomotor processing

During pursuit of a sinusoidally moving dot in phase with coherent motion of a parametrically modulated amount of background dots the most prominent activations could be seen in MT+ Existing constant activations could be due to ocular motion information which does not change across the stimulation The pCG was also constantly active. The posterior cingulate is thought to play a role in integrating sensory and motor signals to guide ongoing eye movements (Berman et al., 1999a; Olson et al., 1996). The other oculomotor output signal activations where constantly quite small and often sub threshold at FWE correction threshold. In humans MT+ has been described to participate in processing of eye movement information (Dukelow et al., 2001; Goossens et al., 2006; Huk et al., 2002). The small activation could eventually be explained by the fact that retinal slip was very small during optimal pursuit. An increase of activation which could result from an increasing retinal error due to more background dots could not be seen, except in basal visual areas. Surprisingly we did not find any dorsal PPC activation in this stimulation type. This fact is very interesting since it is known that PPC is coding motion in space (Andersen, 1997; 1998; Grefkes and Fink, 2005). Thus, we could even have expected that PPC activation increases with more moving background dots. Also in this stimulation type basal visual areas seemed to be less sensitive to motion than MT+.

Visuo-oculomotor processing

During pursuit of a moving dot during the presence of parametrically modulated amounts of stationary background dots significant activation was found in similar areas as in the oculomotor condition; but those activations were in general stronger than the activations of

the oculomotor stimulation. This result could be explained by the fact that in this stimulation type a mixture of effects could have taken place. This mixture could consist in an activation increase at lower level (retinal) and a more constant activation due to eye movement information which did not change across the parametric modulation.

The effect that until the amount of 16 background dots in most of the cortical regions the activation increased similarly to the visual stimulation but that activations in MT+ V7/LOP and PPC were smaller and increases less prominent than in the visual stimulation was surprising (since we expected the similar increase in retinal stimulation of the visual and the visuo-oculomotor task to yield similar activation patterns in visually activated regions). A possible explanation could be pursuit compensation for the retinal error during eye movements. It is known from monkey studies that the brain compensates for induced motion in the opposite direction of pursuit (Morvan and Wexler, 2005) e.g. in MSTd (Shenoy et al., 2002). Thus, most of these retinal image/ optic flow impressions are ignored (Lindner et al., 2001). This might reduce activations in other cortical areas as well.

The fact that basal visual areas are more activated by eye movement tasks than by purely visual stimulation substantiates the supposition of our previous experiment (Kimmig et al., in revision) that they might process extra-retinal information as well. Recently, V1 activation in a saccade task has been found to be related to spatial updating (Merriam et al., 2007)

Processing of 36 background dots

In comparison to the 16 background dot conditions a background of 36 dots, moving or stationary, led to a decrease of activation in most of the activated areas in the visual and visuo-oculomotor conditions (Fig. 4; Fig. 5). This decrease was not seen in the oculomotor condition. This result leads to the assumption that if background and eye motion differed in direction, at some stage the increase of activation in correlation to the amount of background dots seemed to have reached a saturation level. This result needs further investigation.

Sensorimotor transformation sites

In the current study we found two areas which seemed to be involved in transformation of visual input to motor output since they were active in all three stimulation types (visual and oculomotor processing; whitish regions in Fig. 6). In our former study (Kimmig et al., in revision, using one background dot in all stimulation types) those areas seemed to be the PPC and MT+. Here, we could confirm that part of the MT+ complex was activated by all three stimuli. The PPC showed a more differential activation behavior and seemed to be more activated by visual and visuo-oculomotor stimulation and only very little by oculomotor stimulation. Furthermore when using more than one background dot we found in addition a more posterior area (V7/LOP) which was constantly activated by all three stimulation types and different amounts of visual dots.

PPC

In previous publications different parts of the PPC in monkey have been described to be multimodal and code the spatial location of visual objects (Andersen, 1997; Bremmer et al., 2002). The ventral intraparietal area (VIP) (for a review see Bremmer, 2005; Schlack et al., 2003) code visual stimuli in eye centered (retinal) reference frames and respond to eye movement signals (head centered reference frame) and other sensory modalities.

In our previous experiment (Kimmig et al., in revision) part of the PPC was activated by visual, oculomotor and visuo-oculomotor stimulation. Here, this part of the PPC seemed mainly activated when visual target and background moved in opposite directions. Thus, this part of the PPC could participate in integrating the movement of the frame of reference in relation to the visual target, which would explain the lack of activation during oculomotor stimulation. In monkey a part of the PPC (VIP) has been suggested to perform this functional role (Bremmer, 2005).

V7/LOP

In the current study an additional region (V7/LOP) was activated by all three stimulation types and thus seems to be a multimodal region processing visual and eye movement information.

MT+

Similar to our previous study (Kimmig et al., in revision) visual motion of one background dot produced very weak activations in the anterior-dorsal part of the MT+ complex in contrast to stronger oculomotor and intermediate visuo-oculomotor activation with one background dot

of most of the MT+ complex (Fig. 6). These results of our last experiment had led us to the assumption that most of the MT+ complex is involved in eye movement processing while visual processing of motion of a single dot hardly activated MT+. It is known that monkey MT+ gets retinal input and extra-retinal input about eye position and is able to process motion in world coordinates (Bremmer et al., 1997; Ilg et al., 2004). Thus, we expected an increase in activation with increasing amounts of dots in the visual motion condition due to stronger retinal input. During eye movement conditions instead, the cortical activation should be independent of the amount of moving dots and involve always most of the MT+ complex.

We could confirm parts of our assumptions in our current study. (i) Activations induced by visual stimulation increased in correlation with the amount of background dots (ii) we found a whitish region of MT+ which was activated constantly during eye movements independent of the amount of background dots. However, this area did not involve the whole MT+ area, but represents supposedly the human area MST (Ohlendorf et al., submitted). Since this area was also activated by the purely visual stimulation here, similar to the above described V7/LOP, a convergence of retinal and eye movement information might take place (visuo- to oculomotor transformation).

However, the function of MT+ seems to be more complex. Purely visual stimulation resulting from motion of 4 and 16 moving background dots led to the largest activation of MT+. These activations were larger than the activation of the other two stimulation types, and involved possibly the whole MT+. Such a differential retinal stimulation has not been shown yet in MT+. It has been shown that human MT is retinotopically organized (Dukelow et al., 2001; Huk et al., 2002) as previously shown in monkeys. The signal seen in area MT+ seems to be an overlay of different effects (retinal, eye movement information). Influence of mechanisms which e.g. compensate for retinal error due to SPEM is possible, however this needs further investigation.

Conclusions

In the current study we could show that areas of the whole SPEM network can be differentially modulated by the amount of background dots depending on retinal or oculomotor information or a mixture of both. Integration of visual and oculomotor information seems to take place in MST and V7/LOP, processing of differential motion of eye and background (reference frame information) seems to take place in the PPC. Surprisingly PPC hardly reacted if eye and background moved in phase. Basal visual areas like V1 seemed to receive extra-retinal (eye movement) information.

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Chapter 6

General Discussion and Outlook

Discussion

When a visual object moves, humans and other animals having a fovea must perform eye movements to track it. With the help of smooth pursuit eye movements (SPEM) the moving object is kept within the fovea, the location of the retina with the highest visual acuity. (Note that in the context of this work exclusively SPEM without movement of the head were investigated). In the last decades the physiological circuits of SPEM have been extensively studied in the monkey with the help of electrophysiological methods (for a review see Thier and Ilg, 2005). In humans they have been studied in patients, which suffered from cerebral lesions (Morrow and Sharpe, 1993; Morrow and Sharpe, 1995; Pierrot-Deseilligny, 1994).
Since the late 1990s it has been possible to examine the whole brain of healthy subjects in the MR-scanner with the help of fMRI. Since then, the cortical areas controlling SPEM in humans could be described (Berman et al., 1999; Petit et al., 1997; Petit and Haxby, 1999). Much less is known about the functional properties of the participating cortical areas, their possible functional subareas, and the functional connectivity of the cortical areas within the SPEM network.
This PhD project aimed to describe the specific functions of motion processing brain regions, the role of visual attention and the transitions from visual to motor information and from retinal to space reference frames. A methodological principle for all studies (except the MT-subregions study, Chapter 4) in the present work were three stimulation types (i) subjects had to fixate a stationary dot, and one or more background dots moved coherently in the horizontal plane (visual stimulation due to the movement of the background dot(s) across the retina) (ii) subjects had to track one dot with their eyes, while one ore more background dots moved coherently in parallel (oculomotor stimulation with only little visual stimulation due to retinal slip), (iii) subjects had to track one dot which moved in the horizontal plane, while one or more dots remained stationary (visuo-oculomotor stimulation due to relative motion of the background dot(s) across the retina plus additional visually driven pursuit motor activity).
In the first study of the project (SPEM–study, Chapter 2, Kimmig et al. in revision) the visual and motor components of the cortical control of SPEM were investigated. It was shown that the sensory input processing during smooth pursuit eye movements was performed in parieto-occipital regions MT+ and part of the PPC, while oculomotor output processing

involved the named areas and, in addition, the frontal regions FEF, SEF, the cingulate gyrus and the precuneus. During SPEM V1 showed activation related to retinal and extra-retinal origin. Furthermore, a part of the basal ganglia (putamen) was shown to play a role in ocular pursuit. Possible sites for visuo-motor transformation or retinal to head/space coordinate transformation could be located in MT+ and in a part of the PPC (possible human correlate of monkey VIP). We suggest that during the transformation process the eye movement signal is continuously transferred to the neurons of the visual map. This updated visual map at the MT+ level can be used to guide the motor output in head/space coordinates. While MT+ is involved in the integration of visual and oculomotor motion signals, the second transformation region which was found, PPC, is capable of integrating polymodal signals (visual, motor, somatosensory, acoustic, effects of attention etc.).

The aim of the second study (Attention-study, Chapter 4, Ohlendorf et al. 2007) was to investigate to which extent visual attention might influence the activity in the cortical SPEM network by modulating focused visual attention.

In this experiment a sinusoidally moving target was presented for pursuit and simultaneously a stationary target for fixation. Gaze could be directed to the pursuit target and attention to the fixation target or vice versa, or gaze and attention were directed to the same – moving or stationary - target. We found that gaze (overt) and attentive (covert) pursuit activated similar regions of the cortical oculomotor network. Gaze pursuit showed higher activations than attentive pursuit. Activations, specific to the dissociation of attention from gaze and independent of eye movements, were found solely in the posterior parietal cortex (PPC). A visual cue indicating a forthcoming attention task activated large parts of the cortical SPEM network, as a kind of preparatory mechanism. We did not find any attention-related regions outside the well-known visuo-oculomotor network. We conclude that attention control during gaze pursuit and gaze fixation occurs within the cortical SPEM network, supporting the premotor theory of attention (Rizzolatti et al., 1987). Attention modulations operate within this network; as a kind of superordinate system they are independent of eye movements, but if eye movements are present attention modulations act on pursuit and saccades in a similar way. Whether, in a divided attention task, continuous attentive tracking is at all possible or whether attention is inevitably shifted between the attention targets remains to be shown in future studies.

The comparison of the results of the SPEM-study (Chapter 2) with the results of the Attention-study (Chapter 3) showed that activations in frontal areas were specifically due to eye movements and only little to attention. The assumption that frontal areas FEF, SEF and pCG were preferentially involved in the processing of the oculomotor output signal could be

confirmed. Furthermore, since the PPC was one area where we could show a more specific processing of attention we could sustain the multimodal character of this area. Here, effectively an attentional signal was supposedly part of the BOLD signal in the multimodal visuo- to oculomotor transformation site.

The SPEM-study (Chapter 2) had shown that the motion sensitive middle temporal area MT+ was differentially activated by visual and oculomotor stimulation. A smaller part of the MT+ region was activated by all three stimulation types (visual, oculomotor and visuo-oculomotor). In monkeys a subdivision of MT+ into MT and MST is mainly based on the different visual properties of these two subregions. We therefore investigated whether the subdivision of MT+ related to visual and oculomotor responses coincides with the MT/MST subdivisions related to the different visual responses. In humans MT and MST subregions have mostly been presented in single subjects using high velocity stimuli. Identification of the subregions in a large sample of subjects has not been performed until now.
In the third study of the project (MT-Subregions study, Chapter 4, Ohlendorf et al. submitted) the visual properties of the human MT+ complex -which is crucial in visuo-oculomotor information processing during SPEM- were investigated. For this purpose optic flow and static visual stimulation in the two visual hemifields were compared. We tested the MT+ complex and its subdivisions in the low velocity range applying optic flow stimuli in and near the visual field centre. We identified two subregions within the MT+ complex on group level. One subregion was activated by ipsi- and contralateral stimulation (supposedly MST) and located in the anterior part of MT+. A second subregion was exclusively activated by contralateral stimulation (presumably MT) and located in the more posterior part of MT+. The primary visual cortex was activated exclusively by motion in the contralateral field, but not by central flow fields. The interactions between MT and MST seemed to function properly even at low stimulus velocities. Furthermore, in contrast to monkey studies the eccentricity of the flow field relative to the midline played a minor role for the location of the MT+ subregions. This result questions the assumed size of MT receptive fields in humans. The particular role of the primary visual cortex in motion processing has to be elucidated in further studies

In the SPEM-study (Chapter 2, Kimmig et al., in revision) we had localized possible visuo-to-oculomotor transformation sites. We assumed that these sites perform an eye motion information update and/or a transformation from a retinal (visual input) to head a centered (motor output) coordinate system. The study showed that primary/basal visual areas like V1 were more activated by eye motion than by visual (retinal motion) i.e. it is possible that V1 is

not only processing primary visual input signals but that rather gets extra-retinal information as well. Since we used a very small/weak visual stimulus in all stimulation types in the SPEM-study, the Multiple-Dots-study aimed to find out more about functional differences in motion and SPEM processing in the visuo-oculomotor transformation regions and the other areas of the SPEM network by varying the amount of coherently moving target dots.

In the fourth study (Multiple-Dots-study, Chapter 5, to be submitted) we investigated activations evoked by visual, oculomotor and visuo-oculomotor stimuli as a function of the amount of visual dots.

Areas of the whole SPEM network showed to be modulated by the amount of background dots. However, these modulations were strongly depending on the stimulation type and varied across the different regions of the SPEM network. Visual input activations increased in correlation with the amount of visual dots, oculomotor output signals seemed to depend on ocular motion information which remained constant in the different eye movement stimulations. The visuo-oculomotor activations seemed to represent a mixture of retinal and oculomotor effects. Visuo-to-oculomotor transformation (integration of visual and oculomotor signals) seemed to be especially processed in MST and V7/LOP, processing of differential motion between eye and background seemed to take place in the PPC. Basal visual areas like V1 seemed to receive extra-retinal (eye movement) information. To understand the functional connections between MST, PPC LOP and V1 still further investigations in humans are needed.

A short overview of the findings in the cortical areas of the SPEM network follows (see also Fig. 2).

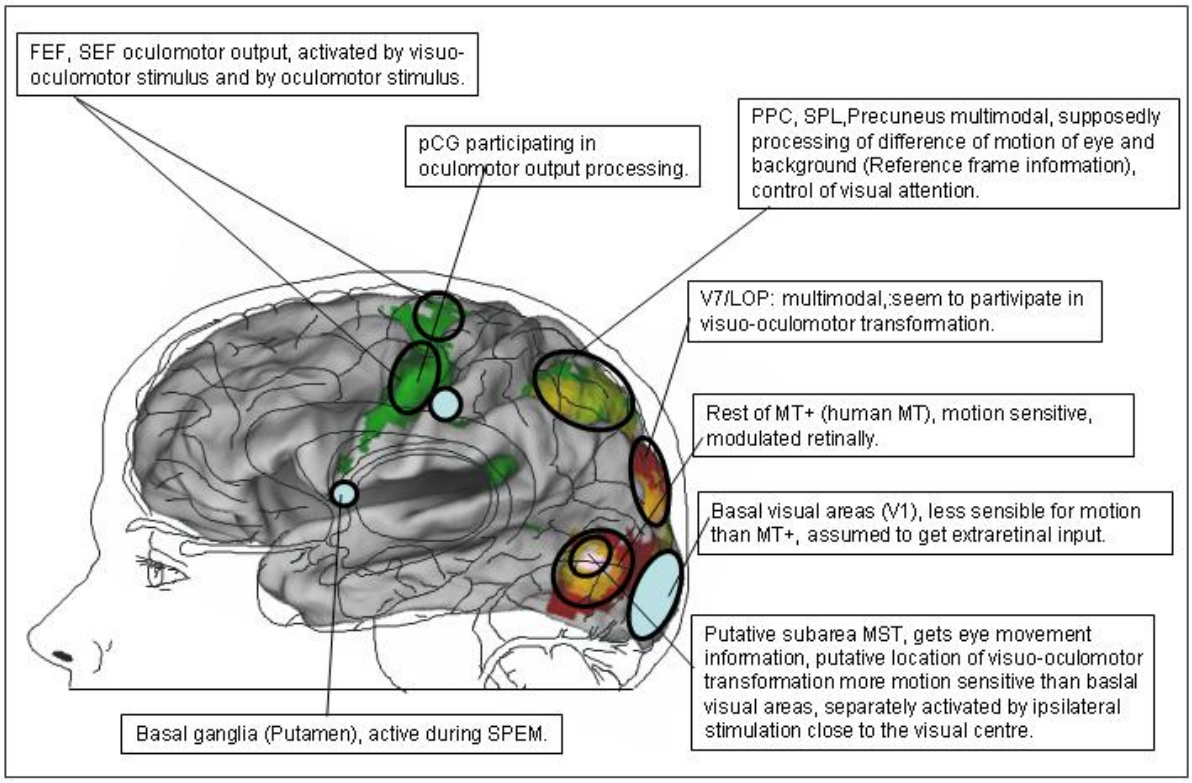

Fig. 2 Overview of functional results of this PhD project. Ellipsoids = functional regions shown on one hemisphere, but active bilaterally; blue colour indicates that the functional region cannot be seen because it is located deeper in the brain or at the medial side of the hemisphere.

SEF: In monkey the frontal eye fields have been shown to facilitate the initiation of SPEM supposedly controlling the gain of SPEM during SPEM initiation (Missal and Heinen, 2001). In the current fMRI studies we confirmed the participation of SEF in the motor output signal in humans (SPEM-study, Chapter2; Attention-study Chapter 3, Multiple-Dots- study, Chapter 5).

FEF: It is known that the FEF participates in the conversion from visual motion into eye velocity (Krauzlis and Lisberger, 1994; Tanaka and Lisberger, 2000). Electrical stimulation of the FEF has shown to evoke SPEM (Gottlieb et al., 1993; Tian and Lynch, 1996) and to increase the gain in SPEM (Tanaka and Lisberger, 2001). In this PhD project, we could confirm a specific processing of SPEM output signals in human FEF (SPEM-study, Chapter2; Attention-Study Chapter 3, Multiple-Dots- study, Chapter 5).

V1: The primary visual area V1 is necessary in the input pathway of visually evoked SPEM. It has been shown that unilateral lesions in V1 abolish SPEM of targets moving in the defective hemifield, contralateral to the side of the lesion (Segraves et al., 1987). In the current fMRI

studies V1 could be shown to be activated by visually evoked SPEM (SPEM-study, Chapter 2; Multiple-Dots-study, Chapter 5) and seemed to get extra-retinal (eye movement) information. However, the region seemed to be considerably less sensitive to motion than MT+ for example. This result confirms indirectly that there must exist a second pathway from the retina leading to MT+ perhaps via the superior colliculus (SC) (Weiskrantz, 1996) or a direct lateral geniculate nucleus (LGN) input to MT (Stepniewska et al., 1999; Sincich et al., 2004) without significant involvement of V1.

PPC: Parts of the PPC have been shown to be multimodal (Andersen, 1997; Bremmer et al., 2001; 2002) and to code motion in space (Andersen, 1997; Bremmer et al., 1998; Bremmer et al., 2001; Grefkes et al., 2004; Ilg et al., 2004). Furthermore it has been supposed that this area is participating in the processing of attention shifts from one visual object to another (Corbetta et al., 2000; Robinson et al., 1995; Yantis et al., 2002) In this PhD project we found a part of PPC being activated by visual and oculomotor stimulation using small stimuli (SPEM-study, Chapter 2). Furthermore it could be shown that PPC was the only area of the SPEM network which was specifically processing visual attention during SPEM (Attention-study, Chapter 3). These results argue for the multimodal character of this part of the PPC. In the Multiple-Dots-Study (Chapter 5) varying the quantity of moving stimuli it seemed that PPC participates in the processing of differential motion between eye and background but surprisingly PPC hardly reacted if eye and background moved in phase. In summary in this PhD project it could be shown that in the PPC different functions can be performed.

V7 and Lateral occipito-parietal area (LOP): In the Multiple-Dots-study (Chapter 5) V7 and part of the LOP were activated by visual and visuo-oculomotor stimulation. In conclusion V7/LOP could also be a possible visuo-to-oculomotor transformation site. In the literature V7/LOP has shown a coarse retinotopy. V7 is upposed to participate in motion and space perception, LOP has been supposed to participate in colour and form perception (Tootell et al., 1998b).

MT+: In single human subjects the motion sensitive region MT+ has been shown in single subjects to consist of at least two subregions MT and MST which are known from monkeys (Dukelow et al., 2001, Huk et al., 2002, Goosens et al., 2006). Subregion MT is located in the posterior part of MT+ and is exclusively activated by contralateral flow field stimulation, MST is located in a more anterior part of the MT+ complex, and is activated by ipsilateral and contralateral stimulation (Dukelow et al., 2001, Huk et al., 2002). In monkey studies it has

been described that receptive fields of MST neurons extend far into the ipsilateral visual field, while the receptive fields of MT cells only extend a few degrees into the ipsilateral visual field (Desimone and Ungerleider, 1986; Gattass and Gross, 1981; Komatsu and Wurtz, 1988; Raiguel et al., 1997; van Essen et al., 1981).

In the SPEM-study (Chapter 2) MT+ was shown to be activated partly by visual and almost completely by eye movement stimulation. Only in a small subarea in an anterior dorsal part of the region activation was obtained by visual and oculomotor stimuli. These results let us assume that the eye movement signal is continuously dispersed across the visual map of MT+ (Chapter 2). This information could be used to update the visual map to the actual eye movement, which is a precondition to encode object trajectories in world centred coordinates.

In the MT-subregions-study (Chapter 3) the MST subregion of the MT+ complex could be localized on group level in the anterior part of the region. The localization of MST in the MT-subregions study was identical with the location of the possible visuo-oculomotor transformation site found in the Multiple-Dots-study (Chapter 5) and very similar to the location found in the SPEM-study (Chapter 2). Since in contrast to monkey studies in our study the eccentricity of the flow field relative to the midline played a minor role for the location of the MT+ subregions our results question the assumed size of MT receptive fields in humans (Chapter 3). Finally, it could be shown that two different functions can be performed in MT+, visual information processing (modulated by retinal stimulation) and eye movement processing (constant during eye movements) (Multiple-Dots-study, Chapter 5).

Basal ganglia (putamen)

The involvement of basal ganglia structures in human smooth pursuit eye movements is a novel finding (SPEM-study, Chapter 2; Multiple-Dots-study, Chapter 5). In monkey, the basal ganglia only recently have been shown to be involved in ocular pursuit (Basso et al., 2005; Cui et al., 2003). Furthermore, putamen neurons have been shown to be strongly active when movements have to be withheld or are self-timed (Lee et al., 2006).

pCG

In the current fMRI studies the pCG showed to be strongly participating in the control of SPEM (SPEM-study, Chapter 2; Multiple-Dots-study, Chapter 5). In the literature the pCG is thought to play a role in integrating sensory and motor signals to guide ongoing eye movements (Berman et al., 1999; Olson et al., 1996).

Until now little is known about the functions of the pCG and the basal ganglia in the control of SPEM. Their role has been neglected and needs further investigation.

Outlook

In this PhD project different functional regions and their role in the cortical SPEM network could be described. In the future we expect better time resolutions, which may allow for more detailed analysis of the SPEM system. By now, this is still difficult due to the limited temporal resolution of the BOLD response (max. at ca. 5 s after an event (Aguirre et al., 1998). In addition, the combination of different methods like fMRI and EEG could enable a more direct look at neural activities occurring in parallel or in certain time courses at different cortical locations with a higher temporal and spatial resolution. Furthermore, fMRI measurements are extremely vulnerable to head motion. Thus, eye movement- investigations in the MR-scanner were only possible by avoiding head movements. However, with a new optical motion tracking method it is now possible to correct externally for head movements in the scanner. This method will allow for detailed investigations of, for example, the cortical representation of different reference frames (e.g. eye centered/retinal, head centered, body centered), which is extremely important for the understanding of eye movement processing. A comparison of fMRI measurements with and without head movements can also help to elucidate the astonishing activations of the PPC seen in the present work and to find out the exact functional role of primary visual area V1 in SPEM processing.

Another interesting aim will be to find out more about functional connectivities of regions of the SPEM network, especially to investigate which connections get stronger and which get weaker during performance of different eye movement and visual tasks. Recent statistical methods like dynamic causal modelling (DCM) can help to obtain more information about the interaction of cortical regions e.g. PPC, MT+ and FEF.

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Education

July 2003 - present	
PhD student	Faculty of Biology Freiburg, Faculty of Biology Basel. Scientific research performed in Dep. of Neurology, University Hospital Freiburg and Dep. of Neuroradiology University Hospital Basel
July 2001	
Degree in Biology and French	Albert-Ludwigs-University Freiburg
1997 – 2001	
Studies	in Biology and French (lectureship) Albert-Ludwigs-University Freiburg
1996 - 1997	
Assistant teacher	High School “La Haie Griselle”, Gérardmer, France
1993 - 1996	
Studies	in Biology and French (lectureship), Philipps University Marburg
1993	
A-levels	Main Subjects: Languages and Sciences

Employment History

2007	Department of Diagnostic Radiology
Research assistant	Medical Physics University Hospital Freiburg
2003	
Research assistant	Research Group Hubert Kimmig PhD, Department of Neurology, University Hospital Freiburg

2002	
Research assistant and Administration	Biological Research Station “El Frio”, State of Apure, Venezuela
2001- 2002	Department of Neurobiology and Zoophysiology, Faculty
Scientific assistant	of Biology, Albert-Ludwigs-University Freiburg

Professional Experience

2006	
6 week supervision of undergraduate practical	“Großpraktikum Neurobiologie”
2003	
6 week fMRI working experience	Research Group of Prof. Mark Greenlee, Abteilung Kognitionsforschung Institut für Psychologie University of Oldenburg
1998 - 2002	
Undergraduate support in different courses	Botany, systematic Zoology, Neurophysiology, Tutorial of Physiology of Sensory Perception (full responsibility)
1999, 2001	
Co-organizer of holiday-courses for grammar school students	teaching French, ‘German, Foreign Language’ and ‘Methods of Learning’

Computing Experience

Operating systems	Windows, Linux
Software	Matlab, SPSS, MS-Office product suite
Brain Imaging + Eye Tracking Analysis Software	SMP2, SPM5, Brainvoyager, Labview

Languages

German	Mother tongue
French	Fluent, teacher degree
English	Fluent
Spanish	Fluent