Functional correlates of the physical and perceptual properties of coherent visual motion in humans

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Barbara Händel,
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1 Introduction

1.1 Background

Perception depends on active physiological processes and is not simply 'picked up' passively by our sensors (Helmholtz, 1866 vs. Gibson, 1950; as cited by Gregory, 2004). Interestingly, this view, even though today commonly accepted, is not intuitive at all since we cannot derive information about the internal processes of perception from introspection. "Moreover perceiving objects around us seems so simple and easy! It happens so fast, and so effortlessly it is hard to conceive the complexity of the processes that we know are involved." (Gregory, 2004). Sophisticated methods had to be developed in order to gain insight into processes associated with perception. One domain which has been investigated extensively in the past is the visual system with a special focus on motion perception. Studies combining electrophysiology and psychophysics in non-human primates have provided remarkable insights how properties of single neurons can contribute to the perception of visual motion.

In primates, area V1 (striate cortex) has been identified as the first cortical area to feature motion direction selective neurons i.e. cells that code for the direction of motion by increasing their firing rate if their preferred motion direction is presented compared to the opposite (unpreferred) one (Hubel and Wiesel, 1968). Specific aspects of visual motion are further processed in subsequent areas. The middle temporal area (MT/V5), first described by Allman and Kaas, (1971) and Dubner and Zeki (1971) with its high percentage of motion selective cells (> 90% cp. <15% in V1, Maunsell and van Essen, 1983) is believed to process rather complex motion, like motion embedded in noise and strong evidence has been accumulated that MT responses are tightly linked to the perception of motion direction.

The general idea concerning the mechanism of visual motion perception suggests the following: direction selective neurons that encode e.g. rightward motion show a higher firing rate if stimulated with rightward motion compared to leftward motion. At the same time neurons coding for leftward motion will fire less if confronted with rightward motion. If now the two firing rates are compared, the rightward neurons exhibit the greater activity and consequently motion to the right is perceived. More specifically, it has been proposed that the neuronal signal coming from area MT's direction selective cells is accumulated over time until responses for one direction reach a certain threshold (Shadlen and Newsome, 2001). This direction can then be communicated by initiating a certain motor response (see Fig. 1).

A large difference in firing rate between two opposite directions is further believed to facilitate the discrimination and to stabilize the percept. In single cell studies neurons are usually measured with one of two motion directions at a time, the preferred or unpreferred one, respectively. Comparing these responses is argued to be equivalent to comparing two neuronal groups with opposing direction preferences. Following this idea, the firing rate induced by the preferred and unpreferred direction of neurons in monkey area MT was compared and it was tested whether the size of the difference correlated with the monkeys' percept. In order to investigate if the discrimination of motion is linked to the different firing rates of MT neurons the difficulty of the perceptual decision had to be varied in a controlled fashion. This could be achieved by adding noise to the stimulus an idea derived from signal

detection theory stating that a feature is detected more easily if the signal to noise ratio is high.

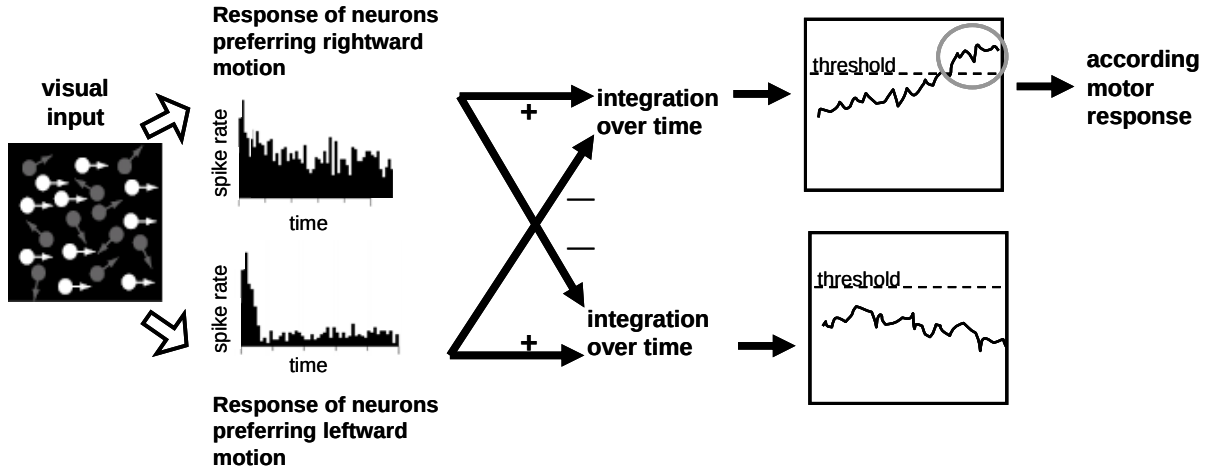

Figure 1) Model of forming a decision about the motion direction. After the onset of the visual motion (input) neurons in the motion processing area will respond according to their preferred direction i.e. increase their firing rate if their preferred direction is prevalent. Exemplary neuronal responses are depicted for two neurons with the preferred motion directions to the left and right, respectively. Responses are further subtracted from each other and integrated separately over time. If the signal for one of the two possible directions passes a certain threshold as indicated by the grey circel, this direction can be communicated via a motor response.

With respect to visual motion the standard paradigm was introduced by Newsome and Paré (1988). In their paradigm a display with randomly placed dots is presented in which a certain percentage of dots moves coherently to one direction (% of motion coherence) whereas the rest of the dots moves incoherently to all other directions (see Fig. 2). The size of the signal is defined by the percentage of coherently moving dots whereas those dots moving incoherently compose noise disturbing the detection of the global motion direction.
In human as well as non-human subjects, perception has been found to be more accurate, i.e. more correct judgments about the global motion direction are achieved, the higher the motion coherence is (see e.g. Newsome and Paré, 1988). In line with the above stated ideas an increased difference in responses of direction selective neurons to preferred compared to unpreferred stimuli with rising motion coherence has been found in various cortical areas (MT: Britten et al., 1992; Newsome et al., 1989; Britten et al., 1996; lateral intraparietal area: Shadlen et al., 1996; 2001; Roitman et al., 2002 and prefrontal areas including the frontal eye field: Kim and Shadlen, 1999). Specifically, motion in the preferred direction of the measured neuron increased the firing rate in extrastriate MT neurons with rising motion coherence but increasing coherence in the unpreferred direction did not change the neuronal response rate (Newsome et al., 1989). Consequently, the difference between opposing neuronal signals increased in parallel with the ability to perceptually differentiate between these two signals.
The results by Newsome and colleagues further indicated that the sensitivity of neuronal activity in area MT equals the sensitivity of the psychophysical judgment since the answer of a single cell to changing motion coherence behaved very similar to the observerd change in the perceptual decision. Whether or not responses of single neurons in area MT to random dot

stimuli carry directional signals of sufficient precision to completely account for the psychophysical sensitivity to visual motion as indicated by their study is, however, still under debate (Cook and Maunsell, 2002).

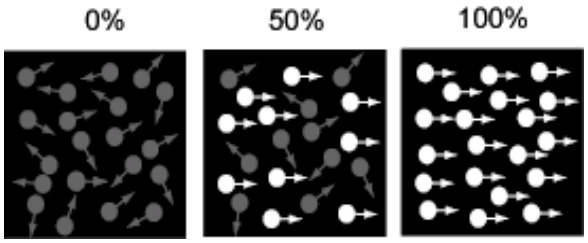

Figure 2) Examples of a random dot kinematogram with three different motion coherence levels (defined by the percentage of coherently moving dots). Motion direction of the individual dot is indicated by the pointing direction of the arrow and dots moving coherently to the right are colored white while incoherently moving dots are colored grey for demonstration. The first example shows incoherent motion (0% coherence) = only noise; the second one 50% coherence and the third example 100% coherence = only signal.

Unfortunately, human experiments are far from providing such detailed insight in the neuronal mechanism underlying motion perception. The main problem of human studies seems to differentiate between neuronal answers that encode specific information as e.g. the direction of motion. In the above mentioned monkey studies single cell activity elicited by visual motion in the preferred as well as unpreferred direction was collected and could be correlated with the two possible answers in a two alternative forced choice paradigm. Due to limitations of noninvasive imaging techniques applied in humans only large populations of cells can be measured. Even though neurons encoding the same direction are arranged in motion columns (Albright et al., 1984) it is impossible to differentiate between opposing signals due to the fact that these motion columns are smaller than the spatial resolution of the imaging techniques applicable in humans.

One main goal of the work at hand was to employ a paradigm which renders the differentiation between responses elicited by opposing motion directions unnecessary but will still allow to look for a correlation between the neuronal representation of the relevant signal and the perceptual decision. The idea was the following: In a paradigm as the one described above where a random dot display is varied in motion coherence and subjects have to detect a global motion direction incoherent motion resembles noise and coherent motion the signal. An increase in brain response with rising motion coherence consequently traces the increase in the signal to noise ratio and should be paralleled by an improved percept. Importantly, this will be true no matter what the specific motion direction is. The work at hand confirmed coherence modulation in human extrastriate cortex using magnetoencephalography (MEG) and utilized this response modulation to explore several questions about perceptual processes related to visual motion in the human brain.

1.2 Questions

1. Single cell responses in monkey area MT correlate positively with motion coherence, can the same dependency be found in human extrastriate areas using MEG? A special interest lay on a full description of the influence of motion coherence on oscillatory brain activity.

2. Coherence dependent modulation might depict the ability of the cortex to differentiate between signal (coherent motion) and noise (incoherent motion) thereby providing an indicator for the accuracy of percept.

   A) Attention can improve motion perception in a noisy stimulus. Is a perceptual improvement due to attention paralleled by an increased strength of coherence dependent response modulation?
   B) Patients with cerebellar lesions show visual motion perception deficits. Concerning motion stimuli embedded in noise, these patients need a higher percentage of coherent motion in order to perceive the global motion direction. Is this deficit paralleled by a decreased motion coherence dependent modulation of cortical activity?
   C) If coherence modulated response amplitudes indicate the signal to noise ratio, correct trials might exhibit different responses compared to incorrect ones. Does neuromagnetic activity showing coherence modulation also differ between correctly vs. incorrectly answered trials for a given coherence level?

3. A further aspect of the work addressed the question if the same network that underlies perception of real motion is also involved if illusionary motion is perceived.

   A) Does the motion aftereffect (MAE) change activity in motion coherence dependent cortical areas?
   B) Do patients with cerebellar lesions also exhibit an altered MAE in parallel with their impaired ability to perceive real motion?

1.3 Overview

1.3.1 Opposite dependencies on visual motion coherence in human area MT+ and early visual cortex

While single cell recordings in non-human primates have consistently demonstrated that activity of most neurons in the middle temporal area (MT) reflects the strength of visual motion by increasing their firing rate align with increasing motion coherence (Britten et al., 1992; Newsome et al., 1989; Britten et al., 1996) human studies are still discordant about a coherence dependent modulation of activity in human visual areas. On the one hand, Rees et

al. (2000) using functional magnetic resonance imaging (fMRI) and Aspell et al. (2005), Nakamura et al. (2003) and Siegel et al. (2007) using MEG could show a positive correlation between motion coherence and activation in area MT+, a complex of various extrastriate areas including area MT and MST (medial superior temporal area). Likewise, Braddick et al. (2001; fMRI) and Maruyama et al. (2002; MEG) observed a stronger MT+ activation for coherent as compared to incoherent motion. On the other hand, however, some studies found no or even a reverse relationship between motion coherence and activity in MT+ (fMRI: McKeefry et al, 1997; MEG: Lam et al., 2000).

The first study presented here was performed in order to test if motion coherence dependent modulation can be found consistently in human area MT+. A second aspect of this work was to provide for the first time a full description of these dependencies with respect to oscillatory activity within brain responses. To this end, human whole brain activity was measured using MEG while subjects had to discriminate the global motion direction (left or right) of a random dot kinematogram (RDK). In a first experiment (n=8) this RDK was presented in the left visual hemifield whereas in a second experiment (n=8) the RDK was shifted to the opposite side. The strength of the motion signal was systematically varied by the percentage of coherently moving dots and the task applied was designed as a modified delayed match-to-sample paradigm where motion direction had to be compared to the pointing direction of an arrow presented at the end of the trial. This design allowed disentangling visual stimulation from motor response preparation. Moreover, by excluding eye movement dependencies on motion coherence, changes in the neuromagnetic responses could be attributed to changes directly related to the cortical processing of the physical attributes of the motion stimulus.

As a first result it could be shown that RMS values i.e. the averaged and not specifically filtered neuromagnetic activity, linearly increased with rising motion coherence. The earliest response depending on motion coherence could be attributed to human area MT+ using a conservative equivalent current dipole model, replicating results by Aspell and colleagues (2005).

Interestingly, two magnetic signals oscillating in separate frequency bands were found to also modulate their amplitude in dependency on motion coherence. First, a slow frequency oscillation within the delta band (1-3 Hz) showed a linear increase in amplitude with rising motion coherence and was found to have a similar occipito-temporal sensor distribution as the RMS values pointing to area MT+ as part of the underlying source. This slow frequency oscillation was present during the whole trial but amplitude modulation was triggered by the presentation of the coherent motion stimulus.

Secondly, spectral analyses disclosed a component to correlate with motion coherence which had not been reported so far in either human or monkey studies. This component, arising from early visual cortex and oscillating in the alpha band (~10 Hz) followed motion stimulus offset and showed a negative correlation with rising motion coherence. In contrast to the earlier notion that alpha synchronization indexes ‘cortical idling’, i.e. a default resting state, it is becoming apparent that alpha oscillations rather indicate an active mechanism of suppression. Klimesch et al. (1999) suggested that alpha synchronization might reflect a mechanism which increases signal to noise ratios within the cortex by inhibiting unnecessary or conflicting processes. In a similar way, increasing occipital alpha activity in early visual cortex seems

ideally suited to protect the integration of visual motion from disturbing input occurring after motion offset.
The reported results could be replicated in two independent series of experiments, strengthening the conclusion that RMS values as well as delta and alpha oscillations are robustly correlated with visual motion coherence. Such coherence dependent modulation could depict the ability of the cortex to differentiate between signal (coherent motion) and noise (incoherent motion) thereby providing an indicator for the accuracy of percept. In order to explore this notion similar paradigms were utilized.

1.3.2 Selective attention increases the dependency of cortical responses on visual motion coherence in man

A general rule in signal detection theory states that an increased proportion of signal compared to noise improves the ability to perceive the signal. Concerning visual motion processing there is strong evidence that the signal to noise ratio of the visual input is depicted in the neuronal answers of certain visual areas. This notion is supported by the finding that increasing motion coherence leads to improved motion detection as well as rising neuronal responses in extrastriate cortex of human (Rees et al., 2000; Aspell et al., 2005; Nakamura et al., 2003; Siegel et al., 2007; Händel et al, 2007, see 1.3.1) and non-human primates (Britten et al., 1992; Newsome et al., 1989; Britten et al., 1996). However, no direct link between the ability to perceive motion and the cortical responses presumably representing the motion signal compared to noise has been shown in humans.
Attention is known to improve perception (see for review e.g. Reynolds and Chelazzi, 2004) thereby offering a way to test if a change in strength of coherence dependent response modulation parallels perceptual improvement due to attention. In order to test this idea, a motion discrimination paradigm similar to the one describe in 1.3.1 was used for which a strong positive correlation between magnetic responses and motion coherence was robustly shown (Händel et al., 2007). The paradigm of the present study comprised of two RDKs (left and right of the fixation spot) with identical motion coherence levels, however, independent motion directions (left or right). Further, an attentional cue was introduced in order to direct the focus of attention to one of the two RDKs. In 80% of the trials subjects (n=7) had to indicate the global motion direction for the validly cued RDK whereas in the rest of the trials the uncued RDK had to be judged. This setup made it possible to compare neuromagnetic activity elicited by an attended and an unattended motion stimulus within the same trial. That the shift of attention induced by the cue was sufficient to change motion perception was indicated by the fact that valid cueing resulted in an significantly better perceptual threshold (19.9%) as opposed to trials of invalid cueing (42.3%). The perceptual threshold was defined as the percentage of coherently moving dots required to obtain 75% correct responses.
Corroborating earlier findings the amplitude of the 3 Hz (+/-2 Hz) oscillation was modulated strongly by motion coherence in sensors lying contralateral to the attended display. The interesting effect in the present study was a striking loss of this coherence dependency in sensors lying contralateral to the unattended display. This means that independent of the absolute location of the sensors the coherence dependent modulation was only present if

attention was focused on the display lying in the visual hemifield contralateral to the sensor location. Investigating this attentional effect more closely it could be shown that if attention was directed to a stimulus with a high coherence level slow wave amplitudes were increased, however, stimulating with low motion coherence led to a decrease in amplitude if attention was directed towards the stimulus.
In order to explain why attentional influence might be different on high compared to low motion coherence levels it has to be considered that attention in general could apply more than one mechanism in order to improve perception i.e. preferred information could be enhanced while any deviating interfering information could be suppressed. Since in the paradigm used here coherent motion always moved in a horizontal direction it might be appropriate for the system to identify all deviating directions as negligible. Feature-based attention such as defined by motion direction has been demonstrated in single cell recordings to differentially modify neural response rates in such a way: those neurons with a preference close to the attended feature experience an enhanced response gain while others for which the attended feature is different from the neuron's preference are reduced in their firing rate (Martinez-Trujillo and Treue, 2004; Treue and Martinez-Trujillo, 2006). In this way, the present observation of a differential change in neural response depending on motion coherence is in line with the concept of a push-pull effect across the population as suggested from single cell recordings.
The presented results indicate that the strength of the prevalent motion coherence dependent modulation of oscillatory activity in the delta frequency band is linked to the percept of coherent motion. In a next step it was tested if a perceptual change induced by other than attention, namely cerebellar impairment, also leads to a change in cortical coherence dependent response modulation.

1.3.3 Deficits in visual motion perception due to cerebellar lesions are paralleled by changes in motion coherence specific cortical response modulation

Unlike the cerebrum the cerebellum is mainly viewed as irresponsible for any particular overt behavior or psychological process but is rather seen as a computing machine which supports the rest of the brain by modulating cortical activity (Bower and Parsons, 2003). If the support provided by the cerebellum is deficient a cortical dysfunction will result.
A well established non-motor deficit prevalent in patients with cerebellar lesions is impaired motion perception as reported independently by different groups (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier et al. 1999; Jockisch et al., 2005). This perceptual deficit manifests itself in such a way that in a random dot display more dots have to move coherently in one direction in order to enable patients to detect the prevalent global motion direction. Motion coherence modulated cortical activity, as measured in area MT+, is believed to depict the cortical representation of signal (coherent motion) and noise (incoherent motion) of the visual input. If the signal to noise ratio, i.e. the modulation dependent on motion coherence, is high percept should be quite accurate, however, if the coherence dependent modulationis is decreased more signal (motion coherence) sould be needed in order to perceive the global motion direction. One reason for the impaired ability to perceive motion

in a noisy display might be that the signal to noise ratio, i.e. the strength of coherence dependent cortical modulation, is decreased in patients with cerebellar lesions. Importantly, studies in the macaque have shown that there exist connections between the cerebellum and the superior temporal sulcus at which caudal part area MT is located (for review see: Middleton and Strick, 2000; Dum and Strick, 2003) describing a possible way of influence.
Using a random dot display with changing motion coherence levels as described in 1.3.1 the perceptual ability as well as the magnetic response (using MEG) was measured of a group of patients (8) with lesions confined to the cerebellum and compared to a group of age matched controls (13). Corroborating earlier results the ability to perceive coherent motion direction was significantly reduced in the patient group. Further, the strong coherence dependent modulation of MEG responses (RMS values) in healthy controls could be replicated at the same latency and very comparable sensor localization as in a previously described experiment (Händel et al. 2007, see 1.3.1) again indicating area MT+ as prevalent source. When looking at the patient group a similar response modulation due to increasing motion coherence was present, however, clearly reduced in strength. Altered eye movements were not significantly different between controls and patients and were therefore excluded as cause for these cortical differences.
Interestingly, the difference in cortical activation between patients and healthy controls was not a qualitative one as could be further shown by a correlation between the strength of response modulation, the latency of its maximum and the perceptual ability. Specifically, the stronger and the earlier the maximum of the coherence dependent modulation emerged the better perceptual thresholds were achieved. This finding indicates that the prevalent coherence dependent response modulation is indeed linked to the perceptual ability and suggests that the cerebellum supports motion processing by helping to establish cortical responses with a pronounced coherence modulation, equivalent to a good signal to noise ratio.
A quite qualitative difference between patients and controls was found in the spatial distribution of activity reflecting motion coherence. Healthy controls exhibited, after a first modulatory peak in temporo-occipital sensors contralateral to the stimulated visual hemifield, a bilateral coherence modulation starting shortly after motion offset. Cerebellar patients on the other hand did not exhibit such a transfer to the ipsilateral side at any time. A possible explanation could lie in activation of area MST, a motion processing area subsequent to area MT and also part of the MT+ complex. In contrast to the relatively strict contralateral representation of MT neurons, receptive fields in area MST mostly cover parts of both hemifields (Desimone and Ungerleider, 1986). A unilateral stimulus can hence activate area MST bilaterally in a direct way.
A further difference between cerebellar patients and controls was a significantly reduced overall activity in patients during the last part of the stimulus i.e. when the motion direction of the test stimulus had to be compared to the pointing direction of a presented arrow. During this period the decision about the motor response and its preparation had to be made i.e. what finger must be lifted in order to give the correct answer. The activity level during this time period did not correlate with the individual perceptual deficit and activity difference between groups might therefore depict a rather general change in premotor processing due to altered cerebellar output.

In general, the two studies described above showed that an altered ability to perceive coherent motion can be paralleled by a change in the coherence dependent modulation of visual cortical responses. The magnetic response components affected, however, might differ dependent on the cause of the perceptual alteration. In a next step a direct comparison between correct and incorrect trials was aspired.

1.3.4 Neuromagnetic activity, including RMS values, delta and alpha oscillations, differentiates between correctly and incorrectly perceived visual motion.

One intriguing observation about our perceptual performance is that on times we perceive a certain stimulus correctly whereas on others we are not able to even though we deal with the exact same stimulation. There have been approaches to study brain activity during such situations of misperception in human (Shulman et al, 2001; Kompass et al., 2000) and non-human (Bisley et al., 2004; Oliveira et al., 1996; Seidemann and Newsome, 1999; Cook and Maunsell, 2002) primates in order to identify mechanisms which might lead to perceptual errors.

One explanation why some trials are perceived better than other could be a change in signal to noise ratio of the representation of the input. Work above (1.3.1-3) described cortical responses which are modulated by signal strength and altered by the perceptual ability of the subject. The present study was conducted in order to test if these responses dependent on signal strength also differ between correct and incorrect trials despite unchanged stimulation.

Neuromagnetic activity during correctly and incorrectly answered trials was compared intra-individually for near threshold stimulation. Specifically, subjects had to identify the global motion direction present in a RDK and compare it to the pointing direction of an arrow presented at the end of the trial (see 1.3.1). The motion coherence of the RDK was chosen to be low (on average 13+/-6 % coherence) and fairly close to the individual chance level (on average 63 +/-5 % correct answers). Cortical responses obtained from correctly vs. incorrectly answered trials were compared and interestingly, all three components which have been previously reported to be influenced by motion coherence (Händel, et al., 2007, see 1.3.1), namely the RMS values and the amplitudes of delta and alpha oscillations, also exhibited significant differences between correct and incorrect trials.

Specifically, significantly lower amplitudes were found for correctly compared to incorrectly answered trials in the 3 (+/-2 Hz) frequency band. As described in 1.3.2 amplitudes in this frequency band are influenced by the attentional state of the observer and for high coherence levels amplitudes increased with attention but decreased for low coherence levels. Also In the present study effectively focused attention might have caused the correct percept of a trial and consequently also the observed decrease in amplitude could reflect an effect of attention on brain activity. Since the individual stimulation of the present study was of low motion coherence a decrease in amplitude for correct trials was expected if attentional effects are considered to be the cause of the perceptual difference.

Further, a general increase in the RMS values was found for correctly compared to incorrectly answered trials over contralateral occipito-temporal and frontal sensors. The notion that this response corresponds to the one modulated by motion coherence is not supported. In contrast

to the coherence dependent modulation which was completely absent until about 200 ms after motion onset the difference between correctly and incorrectly answered trials started to build up already before coherent motion onset. Additionally, frontal sensors not found to exhibit any coherence modulation showed different responses for correct compared to incorrect trials. The RMS values differing between correct and incorrect trials might therefore rather reflect a fronto-occipital network related to an increase of alertness or temporal expectancy to the onset of the stimulus (Nobre, 2001).
The third component exhibiting a significant difference between correctly and incorrectly answered trials was found to oscillate in the alpha band (10+/-3 Hz). Specifically, bilateral occipital sensors showed a decrease in amplitude for correctly answered trials during the fixation period following the coherent motion presentation with a 200 ms lead of occipital sensors contralateral to the visually stimulated hemifield. Results were interpreted in line with the hypothesis that alpha synchronization indicates an active inhibition of cortical areas (as discussed in 1.3.1). The increased alpha amplitude for incorrect trials might express the attempt to protect visual motion processing from disturbing signals trying to support the percept.
The results so far indicate that the characteristic of magnetic brain responses oscillating in different frequencies can reflect signal strength and the perceptual outcome of a trial. This work further wanted to test if also the interaction between frequency bands can be relevant for perceptual processes.

1.3.5 Cross-frequency coupling of brain oscillations indicates the success in visual motion discrimination

Recent ideas suggest the importance of coupling between oscillations in different frequency bands (Lakatos et al., 2005; Fries, 2005) and experimental indications accumulate that the interaction between slow and fast frequency bands are prevalent in the cortex (monkey: Schanze and Eckhorn, 1997: rabbit: Freeman and Rogers, 2002; and cat: Schanze and Eckhorn, 1997; von Stein et al., 2000; humans: Bruns and Eckhorn, 2004; Demiralp et al., 2006) and of functional relevance.
The general idea behind such frequency coupling might be as follows: slow oscillations can recruit neurons from large brain areas able to transfer information of internal cortical states (von Stein, 2000) to local processes oscillating in a rather fast frequency range (Buzsáki and Draghun, 2004; Basar et al., 2001). Such fast oscillations might be governed by oscillating membrane potentials which alter the spike threshold changing the sensitivity for new input during distinct phases of the oscillatory cycle (Azouz et al., 2000; 2003). In other words, temporal optimization of interaction might enhance the effectiveness of communication thereby improving performance (Lee et al., 2005).
A first experimental hint that this kind of oscillatory coupling might be meaningful with respect to perceptual performance is given by Bichot and colleagues (2005) who reported that in V4 coherence between spikes and oscillating local field potentials (gamma) increased if a stimulus, exhibiting the preferred features of the recorded neuron, has been cued earlier. This

synchronous spiking might have indicated cueing specific attentional processes influencing the percept.
Since robust oscillations were found in the previously used paradigm the hypothesis was tested if the strength of cross-frequency coupling is related to perceptual abilities. Oscillating human MEG signals were investigated with respect to their locking between distinct frequency bands particularly testing possible differences in strength of co-modulation elicited by correctly vs. incorrectly perceived stimuli. To this end a near threshold task (see 1.3.4) was employed which made it possible to analyze perceptually different events at constant stimulation. Data sets are identical to the ones analyzed in 1.3.4.
It could be shown that during the motion discrimination task the amplitude modulation of gamma band activity (63 +/- 5 Hz) was locked to a slow frequency oscillation in the delta band (3+/-2 Hz). The presence of cross-frequency coupling between delta and gamma oscillation is not without precedent in the literature. The specific frequencies for which coupling was found as well as the location of the sensors exhibiting coupling are in line with previous results as reported in animals (Schanze and Eckhorn, 1997; Freeman and Rogers, 2002; von Stein et al., 2000; Lakatos et al., 2005) as well as humans (Bruns and Eckhorn, 2004; Demiralp et al., 2006). In these studies locking was found between slow oscillations (0.1 up to 10 Hz) and gamma oscillations (20 up to 100 Hz). Further, coupling between the two frequency bands was maximal for a phase lag of about half a delta cycle indicating that the amplitude of the gamma oscillation was maximal during the trough of the delta oscillation. Also this result was in line with previous findings (Demiralp et al., 2006; Lakatos et al., 2005).
Most importantly, the strength of cross-frequency coupling between gamma and delta oscillations was increased for correctly answered trials. Specifically, gamma amplitudes were higher during the trough of delta oscillation during correctly compared to incorrectly answered trials in sensors lying over the occipital pole. Comparing gamma and delta amplitudes, averaged over the whole time period were cross-frequency coupling was found, no significant difference between correct and incorrect answers was observed.
The present study indicates that the strength of cross-frequency coupling can be related to the perceptual state of the observer further supporting the concept that not only response strength might influence the effectiveness of processing but also the accurate temporal relation via coupled oscillations.
While studies 1.3.1-4 support the idea that activity in visual cortex modulates with signal strength and is therefore tightly linked to the percept of coherent motion embedded in noise an additional aspect of motion perception was object of the last two studies presented here. Specifically, the difference between motion perception induced by real compared to illusionary motion was investigated.

1.3.6 Gamma oscillations underlying the visual motion after-effect

After having been exposed to strong visual motion in one direction, a subsequently presented stationary visual scene seems to move in the opposite direction. This motion aftereffect (MAE) as first described by Purkinje (1825) and Wohlgemuth, (1911) is usually ascribed to

short-term functional changes in cortical areas involved in visual motion analysis. Single-unit recordings from the visual cortex of monkeys (Petersen et al., 1985; Kohn and Movshon, 2003) and fMRI (Tootell et al., 1995; He et al., 1998; Culham et al., 1999; Taylor et al., 2000) and PET (Hautzel et al., 2001) studies of the human brain have located area MT and neighboring cortex as the major substrate of the MAE. Additional evidence for a role of human MT+ comes from studies using repetitive transcranial magnetic stimulation (TMS) which could show that TMS of human MT+ disrupted the perception of the MAE (Théoret et al., 2002). Area MT+ therefore seems similarly involved in the perception of coherent as well as illusionary motion and the aim of the present study was to investigate if the same oscillatory activity underlies their generation.

To this end magnetic brain responses were measured and correlated to the individual MAE. After a long adaptation phase of coherent motion, a test phase was presented comprising of a display with motion balanced incoherent motion. This incoherent motion was perceived as moving opposite to the test phase direction as a consequence of motion adaptation. In order to estimate the individual strength of the MAE special trials were randomly interspersed. In these trials the normally motion-balanced test stimulus was biased by introducing a variable amount of vertical motion added vectorially to all dot elements using a classical staircase procedure until a point of subjective stability was reached i.e. until subjects reported no net motion (two alternative forced choice: equal number of up and down answers). This approach made it possible to correlate the individual strength of the MAE with the magnetic brain activity. Results were replicated in a second study in which only the location of the stimulus was changed (from the right to the left visual hemifield, n=8+9).

As a first result an electrophysiological correlate of the MAE in form of increased RMS values was observed. By assuming two equivalent current dipoles, a midline source in primary visual cortex, and a second, bilateral source in parieto-occipital cortex close to the location of human area MT+ could be extracted. Only the latter exhibited a significant influence by motion adaptation further supporting, together with earlier findings, the involvement of are MT+ in the perception of real as well as illusionary motion.

Interestingly, the induced MAE was accompanied by a significant increase in gamma-band activity (GBA, 70 – 96 Hz) recorded from parieto-occipital cortex contralateral to the visual motion stimulus, but not related to the size of the MAE measured in the individuals. It has been suggested that the formation of a MAE is accompanied by a decrease in the activity of neurons with a preferred direction matching the direction of the adapting stimulus along with an increase in the firing of neurons, sharing a preferred direction opposite to the adapted one (Mather et al., 1998). Synchronous oscillations between single cells are known to occur more frequently between neurons sharing the same preferences (V1 cat: Eckhorn et al., 1998; Gray et al., 1989; Freiwald et al., 1995 and V1 monkey: Ts'o et al., 1986; Livingstone, 1996; MT monkey: Kreiter et al., 1996). Accordingly, the selective activation of neurons sharing the same trigger feature might lead to increases in synchronous spiking as well as to an amplified formation of GBA without a tight relation to the percept. This concept, however, would also demand an increase in GBA with increased motion coherence. Even though in the studies described above no GBA correlated to motion coherence was found, Siegel and colleagues (Siegel et al., 2007) reported an increase in gamma power with increasing motion coherence if

a very high number of trials was collected and a broad frequency band was chosen in an individually optimized way.
A second, focal GBA response was picked up by the most posterior sensors ipsilateral to the side of the stimulus whose source could not be reliably located. This second GBA focus did show a correlation with the percept and was increased in subjects exhibiting a higher MAE compared to those showing a lower one. Two sources seem conceivable, namely primary visual cortex and the cerebellum. Since dealing with strong visual stimuli the first explanation might seem more intuitive, however, several considerations militate against such an interpretation. 1. TMS of human V1 did not disrupt the perception of the MAE (Théoret et al., 2002). 2. By the same token, the fMRI studies failed to demonstrate MAE-associated BOLD-activations in V1 (Culham et al., 1999; Taylor et al. 2000; Hautzel et al., 2001). 3. The percept related GBA was not observed contralateral to the hemifield stimulated but ipsilateral to it, obviously at odds with the crossed nature of the visual system. An area expected to exhibit an ipsilateral activation because of its crossed connection with the cerebrum is the cerebellum and the consequent concern that GBA reflected hand or eye movements rather than the MAE could be dispelled. This prompts the interesting question, if patients suffering from cerebellar disease might also manifest an altered MAE.

1.3.7 Altered motion aftereffect in patients with cerebellar lesions

It has been shown repeatedly that patients suffering from cerebellar damage are impaired in perceiving global motion direction in a stimulus containing signal (coherent motion) as well as noise (incoherent motion; Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier et al. 1999; Jockisch et al., 2005). Work described above further showed that this perceptual deficit is paralleled by a reduced response modulation induced by signal strength (motion coherence) in extrastriate areas including area MT+ of cerebellar patients (see 1.3.3). The same area is also believed to be involved in the generation of the perception of illusionary motion i.e. the MAE. If area MT+ codes for real and illusionary motion in a similar way altered MT+ activity in patients with cerebellar lesions might not only lead to a deficit in perception of real motion but also to altered perception of illusionary motion. First hints that the cerebellum is linked in the processing of illusionary motion are reported above (1.3.6) describing a correlation between the strength of the MAE and GBA possibly originating from the cerebellum.
In the present study this question was further addressed by comparing the ability to perceive real and illusionary motion between patients with cerebellar lesions (n=12) and healthy controls (n=16) using a motion aftereffect paradigm as described in 1.3.6. As main result patients suffering from cerebellar damage showed a significantly altered MAE compared to age matched controls. Whereas 4 patients out of 11 exhibited a drastic increase of the MAE, one patient showed a complete absence of motion adaptation. By including only those patients in the study who exhibited cerebellar but presumably no other cortical or subcortical deficits, it was secured that the altered percept was not caused by extra-cerebellar modifications. Further, by excluding the possibility that measured group differences were due to difficulties in motor response execution, fixation deficits or nystagmus (a rapid involuntary rhythmic eye

movement) the interpretation was strengthened that the cerebellum did not influence the MAE via an impairment of movement execution.
However, the leading hypothesis how the cerebellum could influence the perception of illusionary motion as described above namely that the altered MAE in cerebellar patients is caused by a decreased ability to perceive motion per se is just as little supported by the present results. First of all no correlation between the judgment about real motion and the percept of the MAE was found. Secondly, such a relationship would rather lead to a reduction in the MAE (i.e. answers close to chance level) than to an increase as mainly observed in this study. So the question remains as to what might be the role of the cerebellum in the MAE.
One function of the cerebellum is believed to be the storage of the expectation of sensory input induced by self movement (Bell, 1981). Resent experiments suggest this sensory predicition to be not just a simple copy of a motor command but a highly adjustable signal reflecting not the motor command itself but the predicted sensory consequences of it, which are dependent on the surrounding (Haarmeier et al., 2001).
This the concept can be extended to sensory predictions during distinct motor states. Prolonged motion stimulation during such a distinct motor state (i.e. fixation) might alter the expectation of the sensory consequences during this state thereby explaining the altered visual percept. Dependent on the alteration, impaired cerebellar processing might lead to a changed MAE: If e.g. the sensory prediction has ceased to be adapted no MAE should be observed. If on the other hand the sensory expectation is strongly adapted a very pronounced MAE should be seen. This idea is in principle compatible with our data since 4 out of 11 patients showed an increased MAE compared to controls whereas one patient showed a significant decrease, namely a MAE close to zero.
Changes in the perception of real and illusionary motion can both be induced by altered cerebellar input although via independent cerebello-cortical interactions.

1.4 Summary

Conform to signal detection theory activity modulated by motion coherence (and therefore associated with the inputs' signal to noise ratio) was linked to the ability to correctly perceive motion direction in a noisy stimulus: spectrally unspecific magnetic field activity as well as oscillatory components in three separate frequency bands were found to be associated with successful motion perception.
RMS value showed a linear increase with motion coherence and could be attributed to visual occipito-temporal cortex including human area MT+. The strength of this coherence modulation as well as its peak latency correlated with the perceptual ability as could be shown by including patients with perceptual deficits as found after cerebellar lesions.
An increase in amplitude with rising motion coherence was also found for low frequency oscillations (~3 Hz, delta) picked up by occipito-temporal sensors. The strength of coherence dependent modulation of this oscillatory component paralleled the perceptual improvement due to focused attention. Specifically, for high coherence levels amplitudes in the delta band were higher for the attended compared to the unattended display but decreased for low

coherence levels. Also incorrect compared to correct trials showed a decreased delta amplitude for low motion coherence stimuli.
These findings indicate that responses modulated by motion coherence are indeed linked to the perceptual ability, however, directly comparing perceived vs. unperceived stimuli reveals further dependencies. Specifically, the amplitude of oscillations within the gamma band (63 +/- 5 Hz) was shown to be locked to the phase of a 3 Hz oscillation. If the stimulus was perceived correctly this cross-frequency coupling proved strengthened.
Additionally, processes not directly linked to the processing of motion and most likely reflecting active inhibition of disturbing signals were shown to correlate with motion coherence. Oscillation in the alpha band (10 +/-3 Hz) showed an inverse dependence on motion coherence within early visual cortex i.e. a decrease in alpha amplitude with increasing motion coherence after coherent motion offset. During this time period also an increase in alpha amplitude for incorrect trials was found.
Last but not least it could be shown that even though responses in area MT+ are associated with the processing of coherent motion as well as the MAE, the percept of real and illusionary motion seem to be mostly independently processed events since the changed perception of illusionary motion in cerebellar patients was not correlated with their impairment to perceive real motion.

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2 Detailed description of the work

2.1 Opposite dependencies on visual motion coherence in human area MT+ and early visual cortex

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Introduction

Sensory information is often unreliable, ambiguous or contaminated by disturbing signals, thus, necessitating a trade off between alternative interpretations in order to come up with a consistent perceptual decision that may guide behavior. One central goal of neuroscience is to uncover the neuronal mechanisms underlying this transformation of noisy sensory information into a uniform percept. In this field of research, combined electrophysiology and psychophysics in non-human primates has provided an excellent opportunity to study how properties of single neurons or of assemblies of neurons contribute to perception. The most intriguing insights in this respect have been gained from studies investigating the mechansims underlying visual motion perception. For this, two-alternative forced choice paradigms requiring the monkey to extract a global motion signal embedded in noise have been used in order to search for neural activity reflecting the physical properties of the stimulus, the animal's perceptual choice, or both. Specifically, by varying the difficulty of the task, i.e. the percentage of elements of the random dot stimulus moving coherently in one direction (motion coherence), it has become possible to compare psychometric and neurometric functions in a quantitative manner (e.g. Newsome et al., 1989). Following this approach, numerous studies have been performed to provide a detailed description of the dependencies of single-cell responses on visual motion coherence with positive (linear) correlations observed in area MT/V5 (MT=middle temporal; Britten et al., 1992, Newsome et al., 1989, Britten et al., 1996), area LIP (LIP=lateral intraparietal; Shadlen et al., 1996 a, 2001, Gold et al., 2003, Roitman et al., 2002), prefrontal areas including the frontal eye field (Kim and Shadlen, 1999, Gold, 2000) and the superior colliculus (Horwitz, 1999). Moreover, responses of neurons in area MT to random dot stimuli have been shown to carry directional signals of sufficient precision to account for the psychophysical sensitivity to visual motion (Britten et al., 1992).

While studies of non-human primates have contributed substantially to our current knowledge of the neurophysiological responses underlying motion perception, human studies measuring brain activity based on the responses of large neuronal populations are far from providing the same quantitative description of brain activity reflecting the physical properties of visual motion. Indeed, imaging studies testing human brain activity as function of visual motion strength are sparse and, moreover, have yielded contradictory results so far. To our knowledge four studies up to now measured brain activations for motion stimuli whose strength was varied systematically and demonstrated a positive correlation between responses of area MT+ and motion coherence (fMRI: Rees et al., 2000; MEG: Nakamura et al., 2003; Aspell et al., 2005; Siegel et al. 2006). While few more studies observed a higher activity in

area MT+ for coherent motion as compared to motion noise (fMRI, Braddick et al., 2001; MEG, Maruyama et al., 2002) other studies failed to reveal this difference or even observed the opposite dependency (McKeefry et al., 1997, Lam et al., 2000). The goal of the present study was to further the characterization of the population responses of motion sensitive areas by measuring how neuromagnetic cortical activity varies with the characteristics of visual motion. Particular emphasis was placed on the spectral analysis of the responses, thus, providing for the first time a full description of the dependencies of spectral powers recorded with whole head magnetoencephalography in man on motion coherence. As will be shown, we observed activations in two frequency domains depending on motion coherence, a first one in the low frequency domain increasing with motion coherence and arising from extrastriate cortex and a second one in the alpha frequency range which could be attributed to early visual cortex and which showed the opposite dependency. From this pattern of results we conclude that the integration of visual motion information over time is protected from disturbing signals via a gating mechanism implemented in early visual cortex.

Materials and methods

Sixteen healthy subjects, six males and ten females with a mean age of 26 +/- 2.9 ranging from 22 to 30 years participated in this study. In Experiment one 6 females and 2 males whereas in experiment two 4 females and 4 males were tested. All subjects had normal or corrected to normal vision. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the guidelines of the local ethics committee of the medical faculty of the University of Tübingen, which approved the study.

Procedure and stimulus material: Subjects were seated upright in a magnetically shielded room (Vakuum- Schmelze, Hanau, Germany) and were instructed to sit as motionless as possible during the MEG recording. Stable posture was supported by a chinrest attached to the MEG chair. The computer generated visual stimuli were rear projected onto a large translucent screen (DLP-projector, frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 92 cm in the magnetically shielded room. Viewing was binocular.

The visual stimulus consisted of 5 periods, each lasting 500ms (see Fig.1) and each being observed by the subjects during controlled stationary fixation. During the first 500 ms, only a stationary red dot (diameter 10 minarc) was presented in the middle of the screen which served as the fixation target and which remained visible for a total of 2 s. The first 500 ms period was followed by a second one introducing a random dot kinematogram (RDK) which covered a square of 16 x 16 deg and was centred 15 deg right (first experiment) or left (second experiment) of the fixation point. The RDK consisted of 1500 white squares (side length = 8 arcmin, lifetime = 1000ms, dot density ~ 6dots/deg^2, luminance 47cd/m^2) all moving incoherently, i.e. in all possible directions with a resolution of 1 degree, at a common speed of 6deg/s. After the presentation of this first RDK that we will also refer to as the "prestimulus", a second RDK, the "test stimulus", started. The properties of this second RDK were identical to those described for the prestimulus except that a certain amount of dot elements moved coherently in the same direction (either to the left or to the right). Specifically, the percentage of coherently moving dots was either 0%, 20%, 40%, 60%, 80%, or 100% of all dots in the individual trial. After a subsequent second fixation period, an arrow was presented in the middle of the screen pointing either to the left or to the right side as

randomly chosen by the stimulus generator. Subjects were instructed to keep fixation as accurately as possible during the whole trial and to indicate by lifting their right or left index finger whether the motion direction of the dots of the test stimulus was identical (right index finger) or opposite (left index finger) to the pointing direction of the arrow. Subjects were instructed to guess if they were not sure about the direction seen (forced choice). Finger movements were detected using a light barrier. Note that the motor response could not be planned until the arrow had been presented, thus, guaranteeing that the MEG signals during the first 1000ms after test stimulus onset were not related to movement preparation. The individual measurement consisted of 720 single trials with each coherence level (n=6) being presented 120 times in a randomized sequence. In order to assess the ability to discriminate the motion direction embedded in noise, the percentage of correct responses in the individual measurement was plotted as function of motion coherence and fitted by a probit function. The perceptual threshold was defined by the coherence level for which the probit function predicted 75% correct responses. In a first experiment (see Fig. 1) eight subjects were measured with the RDKs centred 15 deg *right* of the fixation point. In a second experiment, another group of eight subjects was tested with the motion stimuli presented on the *left* side.

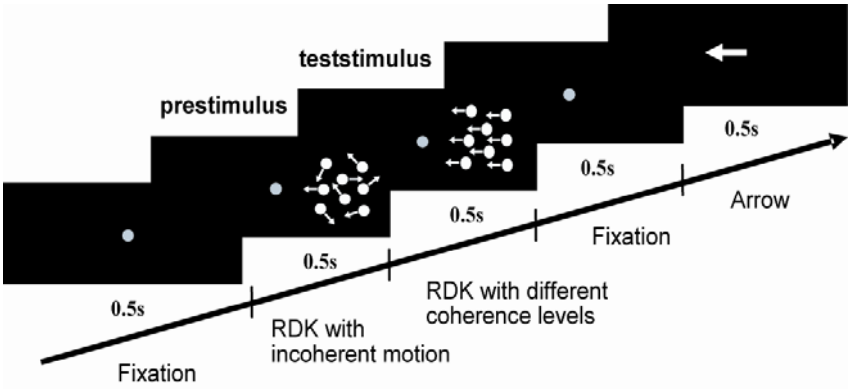

Figure 1) Time course of the stimulus. The stimulus consisted of 5 periods each lasting 500 ms. In contrast to the "prestimulus", a random dot kinematogram (RDK) consisting of incoherent motion, the following "test stimulus" involved the presentation of coherent motion the percentage of which was systematically varied between 0% and 100%. The coherent motion signal was directed either to the left or to the right. Subjects had to indicate whether the motion direction of the coherently moving dots of the test stimulus was identical or opposite to the pointing direction of the arrow presented at the end of the trial. For a first group of 8 subjects, the RDKs were presented right to the fixation dot. A second group of 8 subjects was stimulated with the RDKs located in the left visual field (not shown in the figure).

During all experiments, eye movements were monitored using a homemade video system taking the pupil's center as measure of eye position. Recordings were stored at a sampling rate of 50 Hz and analyzed offline in order to assess the quality of fixation. In particular, the influence of visual motion coherence on the following oculomotor parameters was determined, i.e. slow eye drifts (eye velocity), deviations from the fixation point (eye

position) and the number and amplitude of saccades. To this end, the means of the different oculomotor measures were calculated for each of the 500 ms epochs of stimulation and in each subject. Then, these means were tested for dependencies on motion coherence by one-way analyses of variance performed for each stimulus epoch, separately.

Recording and analysis of the MEG signals: Neuromagnetic activity was recorded using a whole-head MEG system (CTF Inc., Vancouver, Canada) comprising 151 first-order magnetic gradiometers. The signals were sampled at a rate of 625 Hz. Recording epochs lasted from stimulus onset to arrow offset plus 200ms, leaving 2700ms of recording time for each trial. The subject's head position was determined at the beginning and at the end of each recording session by means of localization coils fixed to the nasion and preauricular positions to ensure that head movements did not exceed channel separation.

Analysis of the global field power: In a first attempt to search for MEG activity reflecting the amount of visual motion coherence, we analyzed the global field power (GFP). In order to obtain the GFP, the MEG recordings were first of all baseline corrected with respect to an interval ranging from 240 to 499ms after stimulus onset which corresponded to the second half of the first interval of fixation preceding the presentation of the RDKs. The recordings were then digitally low-pass filtered at 40 Hz and averaged over the 120 trials for each coherence level and each subject using CTF software. Based on these averages, the global field power was calculated for each of the six coherence levels as the root of the mean squared magnetic fields (RMS) of all 151 sensors for each sample and for each subject. Finally, in order to search for dependencies of the global field power on motion coherence, a (running) linear regression was calculated for each point in time testing for linear correlations between the RMS values and the coherence levels (MATLAB, version 6.5.1). Specifically, given the six coherence levels and the eight subjects tested, each regression was based on 48 RMS values. In order to correct for multiple comparisons, at least 15 consecutive p-values of the running regression were required to exceed a 0.01 level of significance (Rugg et al, 1995).

Frequency analysis of the MEG recordings: In order to test whether correlations between MEG responses and visual motion coherence might be confined to specific frequency bands, a spectral analysis of the unfiltered MEG signals was performed. This analysis was conducted on single trial basis in the range of 1–100 Hz (1.23 Hz bins) for five partially overlapping 700 ms time windows. The time windows were defined by the five different 500ms epochs of stimulation (compare Fig.1) each being expanded by the 100 ms interval immediately preceding and following, respectively, the individual epoch. The resulting recording points were reduced to 218 and zero-padded to obtain 256 points. To reduce the frequency leakage the records were multiplied by Welch windows as recommended by Press et al. (1992). A fast Fourier transform was calculated for each time window, each channel and each trial, separately. Then, spectral amplitudes (in the given time window) were averaged over all trials for each coherence level in each subject. The influence of motion coherence on the spectral amplitudes was assessed by an analysis of variance (ANOVA, 6 coherence levels) performed on the unaveraged group of the 8 subjects and for each frequency band (1.23 Hz) and channel (151), separately. Specifically, given the six coherence levels and the eight subjects tested, each ANOVA was based on 48 spectral amplitude values. The p-levels taken to be significant were adjusted by means of a Bonferroni correction given that the p-values of two adjacent frequency bins had to be significant (Lutzenberger et al., 2002). The critical level of statistical

significance was, thus, calculated as p = sqrt (0.05/(number of channels x number of frequency bins))= sqrt(0.05/(151*100))= 0.0019.

Source localisation: As will be described in the Results section, we found that MEG signals in two different frequency domains depended on motion coherence. A first signal was observed in the low frequency domain (1-3 Hz), a second activation oscillated in the alpha band (~10 Hz). In order to localize these two components different methods were used. The reason for chosing different methods for source localization was the following. Event related cortical activity can either be time locked to stimulation and therefore will survive (or will be enhanced by) averaging or, alternatively, may be only losely time locked and, hence, will be detectable only by analyses based on single trials (Klimesch et al, 1998). Evoked cortical activity which is time locked can usually be localised appropriately by applying conventional dipole models. Activity which is not phase locked to stimulation, however, requires alternative approaches of source localization such as offered by synthetic aperture magnetometry (SAM, Robinson and Vrba, 1999). In order to test whether the two MEG signals correlating with motion coherence in this study were either phase locked or not and, thereby, which procedure for source localization would be appropriate, the analysis of variance described above was also applied to the averaged MEG signals.

The effect of motion coherence on the activity in the low frequency domain (1-3 Hz) survived averaging, thus, indicating that this component was phase locked. Accordingly, a conventional dipole model approach was chosen for source localization. Single equivalent current dipoles (ECDs) were estimated for the group averages as well as for the single subjects based on the differences between the MEG responses obtained for the highest (100%) and the lowest coherence level (0%). First, the differences between 100% and 0% were calculated for each subject separately by subtracting the MEG response elicited by the 0% coherence level (raw data was baseline corrected, 40Hz low pass filtered and averaged over trials for each subject separately) from the response obtained from the 100% coherence condition. For the group analysis these differences were then averaged over the subjects. In other words, in a first step only the differential activity was modelled. ECDs were determined by conventional least-square minimization procedures and based on an individual spherical head model, derived from anatomic magnetic resonance images (MRI) of one of the subjects. In a second step and in order to exclude the possibility that the dipole solution derived from the difference between conditions might not be a true reflection of the primary activation or might be specific for the comparison of two extremes, dipole source analysis was also performed for the 100% coherence condition and one further difference (20% versus 100% coherence).

In contrast to the MEG activity in the low frequency band, the alpha oscillation showed a significant dependency on motion coherence only when the signals were not averaged prior to analysis. For this reason, the alpha activation was not considered phase locked and therefore localized by means of a beamformer algorithm. To this end, three-dimensional imaging of brain activity was performed using synthetic aperture magnetometry (SAM; Robinson and Vrba, 1999). SAM is a type of minimum variance beamformer which is sensitive for 4 dimensions (voxel location and source orientation) and therefore might result in a better spatial resolution as compared to conventional beamformers (for details see, e.g. Vrba and Robinson, 2002). This specific type of minimum variance beamformer, implemented in the

CTF software, was calculated for the 9-12 Hz frequency band in the fixation period after motion presentation (1.5 to 2.0 sec). For each subject a pseudo-T statistic was calculated to estimate the difference in source power between the 0% and 100% coherence condition at the given target voxel (voxel side length 1 cm; Robinson and Vrba, 1999).

Results

The results of the two experiments testing MEG responses as function of visual motion coherence were qualitatively the same. This was expected because the two experiments differed only in the visual hemifield stimulated (experiment 1: right hemifield; experiment 2: left hemifield) and were repeated most of all to test the reliability of the results. The similarity of results of the two experiments applied to both the psychophysical/behavioural and the electrophysiological results. More precisely, the motion discrimination thresholds did not differ between the two groups tested as indicated by a group mean being 17.5% in the first and 27.5% in the second group ($p=0.19$). The somewhat higher mean in the second experiment, albeit non-significant, was due to one outlier. Exclusion of this outlier in experiment 2 resulted in a mean of 17.5%, i.e. in the same mean as obtained from experiment 1. Moreover, an influence of visual motion coherence on the quality of fixation could be detected in neither of the two experiments. Specifically, analyses of variance did not show any significant effect of motion coherence on the different oculomotor parameters considered such as slow eye drifts (eye velocity), deviations from the fixation point (eye position) or the number and amplitude of saccades ($p>0.05$, each). In other words, by excluding the possibility that significant eye movements had been elicited by the presentation of the coherent motion stimuli, it was assured that differences in the MEG responses would not reflect oculomotor artifacts. In the following, these electrophysiological differences will first be presented in more detail for experiment 1.

Influence of visual motion coherence on the global field power: As stated in the Methods section, in a first step the global field power (GFP) was analyzed in order to search for MEG activity correlating with visual motion coherence. As shown in Fig. 2A, the power of the global MEG response as assessed by the RMS values started to diverge into higher and lower values for different coherence levels shortly after test stimulus onset. For instance, 210 ms after coherent motion onset, i.e. at the peak latency of the MEG response, the GFP elicited by the 100% coherent motion stimulus was 55% higher than the GFP observed for the 0% coherent stimulus. The positive correlation between GFP and motion coherence which can also be derived from the positive slope (=beta-value) of the running linear regression (see middle panel of Fig 2A) started to be significant 172 ms after test stimulus onset (lower panel of Fig 2A). While this correlation was most robust for the group average, it was present also in the individual subjects as shown in Fig. 2B plotting the GFPs of both the group and the single subjects averaged for a 100ms time interval starting 200ms after test stimulus onset. The same result was obtained from experiment 2 stimulating the left visual field with the one difference that the correlation between GFP and motion coherence emerged somewhat later (254ms after test stimulus onset).

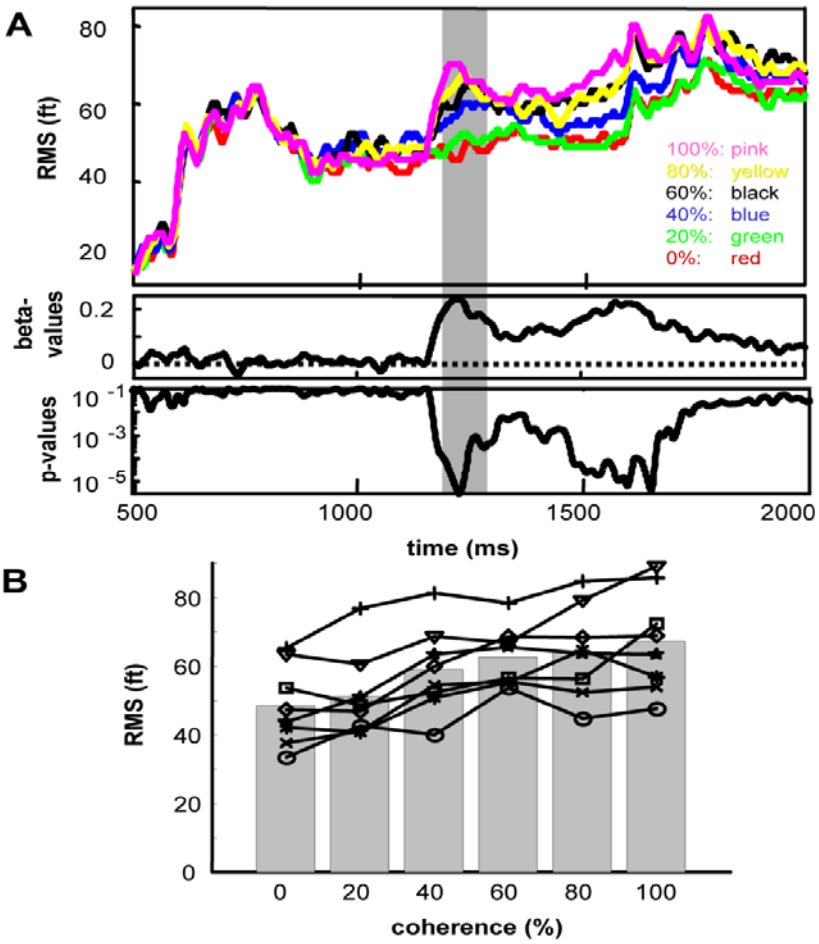

Figure 2) Dependency of the global field power (GFP) on visual motion coherence. A: RMS values averaged over the 8 subjects are plotted for the six coherence levels (indicated by different colours) as function of time. The x-axis starts with the presentation of the first RDK (incoherent motion, onset at 500ms) followed by the test stimulus comprising coherent motion of varied strength (onset at 1000ms). The lower panels show the beta and p values, respectively, obtained from a linear regression between RMS values and motion coherence for each sample point. B: GFP as function of motion coherence averaged for a 100ms interval starting 200ms after test stimulus onset (indicated by the grey area in A). Results of the group (bars) and of the individual subjects (symbols, lines) both reveal a consistent positive correlation between RMS values and motion coherence.

Frequency analysis and source localization: Spectral analysis revealed MEG signals in two different frequency domains depending on motion coherence. A first signal was observed for the time window of test stimulus presentation, a second one in the fixation period following the presentation of coherent motion. The first MEG component was obtained in the 3Hz frequency band and was picked up from temporo-occipital sensors located contralateral to the stimulated visual hemifield (Fig 3A). As shown in Fig 3B, the dependency of the spectral power in this frequency range was positive for these channels, i.e. spectral power increased monotonically with increasing motion coherence similar to the changes in GFP observed in this time window. Indeed, the distribution of the sensors with significant effects (Fig. 3A) resembled very much the magnetic field distribution of the group difference between the MEG responses obtained for the highest (100%) and the lowest coherence level (0%) depicted in Fig. 3C, thus, suggesting that the differences in the GFP reflected this low frequency component. As justified in the Methods section, this MEG signal was modelled by assuming a single equivalent current dipole (ECD) whose three-dimensional location and orientation were estimated by applying the analysis to the difference between MEG signals obtained for the 0% and 100% coherent motion conditions. Dipole solutions were calculated for the grand average of all subjects and, additionally, separately for each subject. As shown in Fig. 3D, the differential neuromagnetic activity observed for the group could be adequately described (i.e. explaining a minimum of 70% variance for dipole fits in single subjects) by assuming a single equivalent current dipole (174ms after coherent motion onset) in left temporo-occipital cortex

(Talairach coordinates: x= -27.5, y= -68.7, z=11.0) close to area MT (V5) + as delineated in numerous imaging studies (e.g. Previc et al., 2000; Watson et al., 1993). Dipole solutions derived from single subjects confirmed this conclusion with coordinates close to those obtained from the group data (x = -24.8 +/- STD 4.4, y = -74.2 +/- STD 7.9, z = 12.4 +/- STD 5.8). Dipoles were located contralateral to the visually stimulated hemifield in all subjects. For 2 subjects no single dipole solution was feasible because the differential activity in these two subjects was too small.

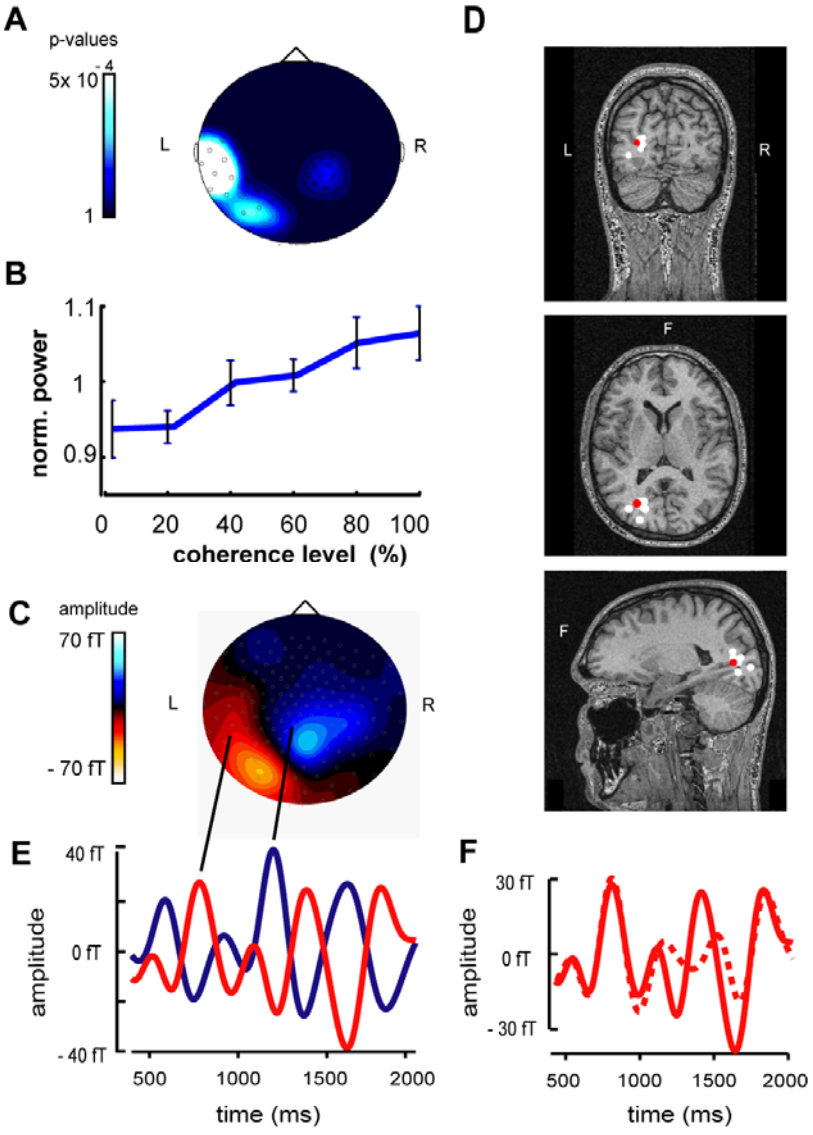

Figure 3) Spectral power in the 3Hz frequency band during coherent motion presentation correlates with motion coherence. A: Statistical probability mapping of spectral amplitude dependencies on motion coherence projected onto a two-dimensional MEG sensor map (seen from above, nose up). p-values denoting the level of statistical significance of the effect of motion coherence on the spectral amplitude were calculated from an ANOVA and are color-coded here in order to provide a quasi-field distribution. R: right. L: left. B: Spectral power in the 3Hz frequency band averaged over all channels with p-values $\leq$ 0.0019 as function of motion coherence. The y-axis denotes the means and standard deviations of the spectral power for the group of 8 subjects. Before assessing the group statistics, spectral amplitudes for the different coherence levels were normalized in the individual subject based on the mean spectral amplitude obtained from all coherence levels. C: Magnetic field map of the group difference between MEG signals obtained for the 0% and 100% coherent motion conditions (166ms after test stimulus onset). D: Dipole solutions of the differential activity depicted in C. The red dot marks the dipole obtained from the group analysis, the white dots delineate the location of dipole solutions derived from 6 out of 8 subjects. (R: right; L: left; F: frontal). E: 3 +/-2 Hz Gaussian filtered time-course of MEG activity recorded from two sensors (marked in 3C with two lines and held distinguishable by two different colors) for the 100% coherence condition. The coherent stimulus started at 1000ms. F: 3 +/-2 Hz Gaussian filtered time-course of activity recorded from the left sensor as depicted in red in figure 3E. The solid line shows the oscillatory activity for this sensor elicited by the 100% coherence condition as compared to the 0% coherence condition (dashed line).

While the variance of the differential magnetic field explained by the dipole model was higher than 70% for the first 230 ms after test stimulus onset the following activity was not

sufficiently explained by a single ECD located in temporo-occipital cortex. The following activity, however, was too variable in the individual subjects to allow for reliable source localization. The dipole fitted to the group difference between the 100% and 20% motion coherence condition (x: -39, y= -64, z: 19.8; 174ms after coherent motion onset; explained variance > 86%) and to the group data obtained from the 100% coherence condition (x: -34, y= -75, z: 13; explained variance > 80%) exhibited very similar coordinates as those derived from the first comparison (difference between 100% and 0% coherence).
The second MEG signal depending on motion coherence was observed in the 10 Hz frequency band and was present only in the fixation period following the offset of coherent motion presentation. This neuromagnetic activity being statistically significantly modulated by motion coherence was picked up from channels covering the occipital region (Fig 4A).

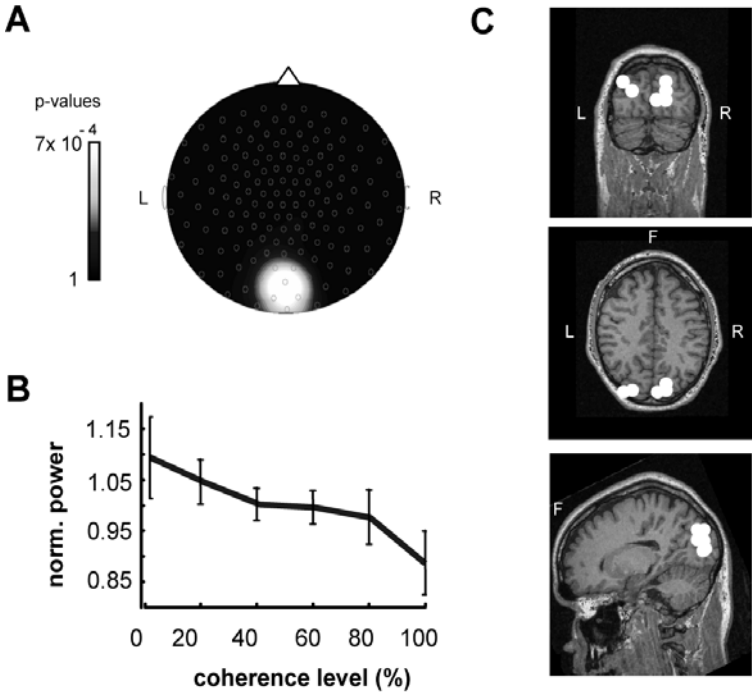

Figure 4) Spectral power in the 10Hz frequency band after coherent motion offset correlates with motion coherence. A: Statistical probability mapping of spectral amplitude dependencies on motion coherence projected onto a two-dimensional MEG sensor map (same conventions as in Fig. 3A). B: Means and standard deviations of the spectral power in the 10 Hz band for the group of 8 subjects as function of motion coherence (same conventions as in Fig. 3B). C: Localisation of voxels with maximum T-values obtained from pseudo-T statistics estimating the difference in source power between the 0% and 100% coherence condition (results from 6 out of 8 subjects). Source power was obtained using a minimum variance beamformer (SAM) for the 9-12 Hz frequency band.

As can be derived from Fig. 4B, the spectral power in the 10 Hz band decreased monotonically with increasing coherence. As explained in the Methods section, instead of a dipole model a beamforming method was used in order to localize this activity. To this end, first the source power was calculated for the 9-12 Hz frequency band during the fixation period after the test stimulus using SAM (for details see methods). Secondly, the difference in source power between the 0% and 100% coherence level was calculated applying pseudo-T statistics. Fig. 4C shows that voxels with the maximum T-values ($T \geq 4.8$) were located in occipital cortex indicating an activation of early visual cortex such as areas V1 and V2 (x = 1.7 +/- STD 22.2, y = -88.2 +/- STD 6.12, z = 15.2 +/- STD 10.1). For 2 out of 8 subjects SAM revealed no voxels with significantly higher activations for the incoherent motion condition. No effects could be found in the theta or beta frequency range.

Experiment 2 in which the visual motion stimuli were presented in the left hemifield replicated the results of the first experiment. Briefly, the two main observations, i.e. demonstration of neuromagnetic activity in the 3 Hz frequency band positively correlating with motion coherence and of a second activity in the alpha band negatively correlating with motion coherence were replicated (Fig. 5). Identical to experiment 1, the low frequency activity was present during motion presentation whereas the alpha modulation was observed after motion offset. Dipole solutions again suggested contralateral area MT(V5)+ as the main neuronal substrate of the low frequency activity (x =26.7 +/- STD 7.5, y = 71.3 +/- STD 15.9, z = 10.9 +/- STD 10.1). Dipoles were located contralateral to the visually stimulated hemifield in all subjects. In turn, the alpha activation could be attributed to early visual cortex ($T \geq 1.9$; x = 9.4 +/- STD 8.9, y = -92.7 +/- STD 11.1, z = 9.6 +/- STD 15.3) with the one difference to experiment 1 being that it seemed to be more clearly confined to the hemisphere contralateral to stimulation. For 3 out of 8 subjects SAM revealed no voxels with significantly higher activations for the incoherent motion condition. Finally, in neither experiment 1 nor experiment 2 any neuromagnetic activity in the gamma range was observed correlating with motion coherence as might have been expected considering the work of Siegel and collegues (2006).

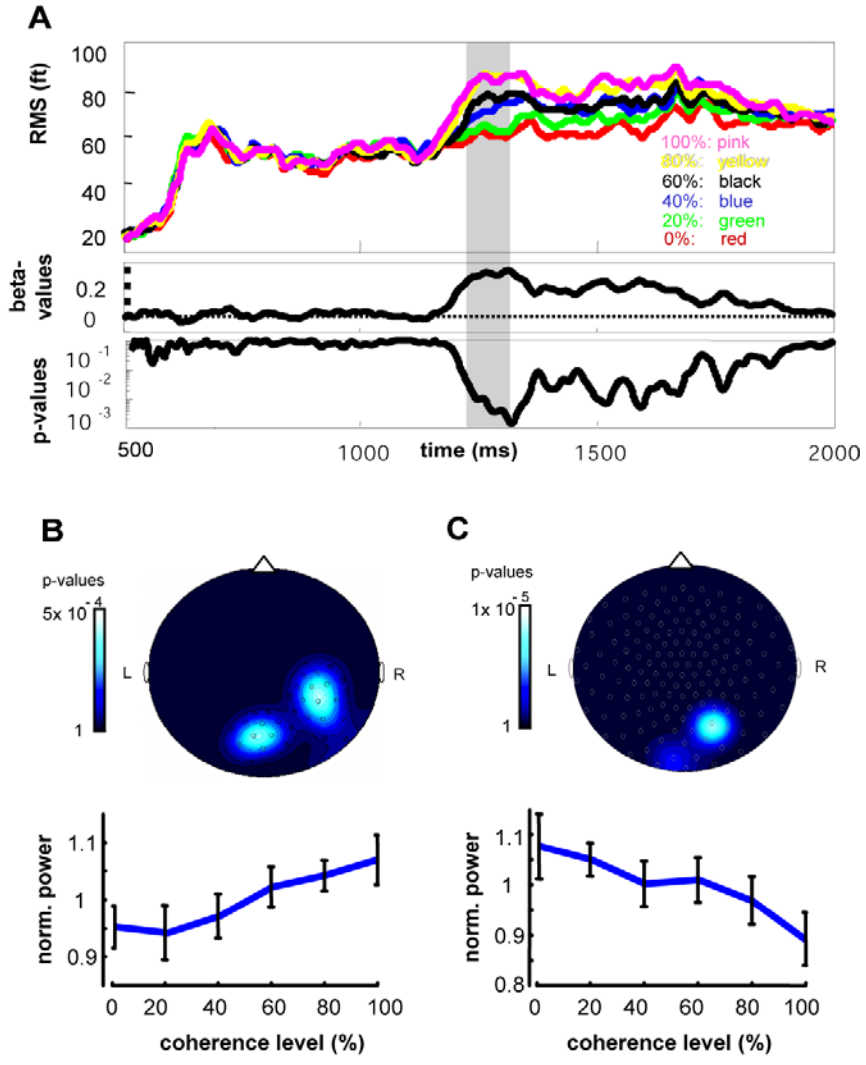

Figure 5) Correlations of spectral power with motion coherence for experiment 2 (visual motion presented in the left hemifield). A: Spectral power in the 3Hz frequency band during coherent motion presentation positively correlates with motion coherence. B: Spectral power in the 10Hz frequency band after coherent motion offset negatively correlates with motion coherence. Upper panels: Statistical probability mapping of spectral amplitude dependencies on motion coherence projected onto a two-dimensional MEG sensor map (same conventions as in Fig. 3A and 4A). B: Means and standard deviations of the spectral amplitudes for the group of 8 subjects as function of motion coherence (same conventions as in Fig. 3B and 4B).

Discussion

While single cell recordings in non-human primates have yielded intriguing insights into the mechanisms underlying visual motion perception by testing how neuronal responses of selected cortical areas vary with the characteristics of visual motion, human studies measuring brain activity as function of motion strength are rare. This study was performed in order to provide for the first time a full description of the dependencies of spectral powers of brain activity on motion coherence in man. To this end, a modified delayed match-to-sample paradigm was chosen which allowed to disentagle visual stimulation from motor response preparation. Moreover, by excluding eye movement dependencies on motion coherence, changes in the neuromagnetic responses could be attributed without doubt to changes directly related to the cortical processing of the physical attributes of the stimulus. Finally, the results could be replicated in two independent series of experiments, thus, extensively excluding the possibility of statistical errors due to multiple comparison inherent to human brain imaging studies.

A first finding of this study was that neuromagnetic responses attributed to human area MT+ linearly increased with motion coherence. At first glance this result may not be surprising since MT neurons have been shown to linerally increase firing rate with motion coherence in various single cell recording studies (e.g. Newsome et al. 1989, Britten et al. 1992, Britten et al. 1998, Maunsell and Van Essen 1983; Zeki 1974). Yet, human studies performed so far have not consistently demonstrated that activity of human area MT+ reflects the strength of visual motion. On the one hand, Rees et al. (2000) using fMRI and Aspell et al. (2005) using MEG could show a positive correlation between motion coherence and activation in area MT+. Likewise, Braddick et al. (2001; fMRI) observed a stronger MT+ activation for coherent as compared to incoherent motion. On the other hand, however, some studies found no or even a reverse relationship between motion coherence and activity in MT+ (fMRI: McKeefry et al, 1997; MEG: Lam et al., 2000).

The differences between the results of these studies might at least partly be explained by stimulus parameters (e.g. dot density) as discussed in detail by Braddick et al. (2001). Low dot densities such as used by McKeefry et al. (1997) or Lam et al. (2000) who demonstrated higher activations for noise stimuli might not be sufficient for summation of the response under the coherent motion condition. In line with this interpretation, the dot density used here was roughly 30 times higher than the one used for instance by McKeefry et al. (1997). As discussed by Aspell et al. (2005) also stimulus size may play an important role. The reason is that visual stimuli used in human studies are not confined to the classical receptive field of neurons in area MT, i.e. for the majority of neurons at least parts of their surrounds are stimulated with the consequences of center surround interactions which on average may tend to be inhibitory (Allman 1985, Born and Tootell 1992). We can not validate this hypothesis since our stimulus (16°) exceeded the mean receptive field size (9°) of monkey MT for the eccentricity chosen (Albright and Desimone, 1987). In summary, dot density rather than stimulus size seems likely to have important influences on the differential population responses to visual motion but their specific impact remains to be specified by further studies.

Most of the human studies addressed so far found more areas than area MT+ alone to be influenced by motion coherence including area V3a, the intraparietal and superior temporal sulcus (Braddick et al., 2001 and Aspell et al., 2005), or area V1/V2 (McKeefry et al., 1997).

Rees et al. (2000) supplying the most detailed description of dependencies of BOLD responses on motion coherence so far reported bilateral activity in areas MT+, KO (KO=kinetic occipital) and V2 as well as activation in the right fusiform gyrus, left occipital gyrus and left middle occipital gyrus to increase for higher motion coherence. Conversely, activity in right anterior cingulate and left insula was found to negatively depend on motion coherence. As stated in the Results section, also in this study the brain activity reflecting motion coherence was not restricted to area MT+ because correlating responses were observed more than 230ms after test stimulus onset, i.e. definitely after the interval for which the differential activity could be sufficiently modelled by a single (MT+) dipole. This correlating activity following the MT+ response, however, could not be adequately localized due to large individual differences and low signal to noise ratios.

An increase in activity by motion coherence could not only be shown for the RMS values (i.e. activity averaged over trials) but also for the raw data in a 3 Hz frequency band. In order to test whether this latter effect was a reflection of a sustained slow frequency oscillation or, alternatively, a classically evoked potential, we looked at the time course of the 3 +/- 2 Hz Gaussian filtered MEG signals as exemplified for two channels (LT25, RP11) in Figure 3E. As can be seen from this figure, the 3Hz oscillations already started during the presentation of the incoherent motion (onset: 500ms), persisted at least until the end of the second fixation period (2000ms) and therefore did not reflect motion stimulus on- or offset. Its modulation (see Fig 3 f), however, was triggered by the presentation of the coherent motion stimulus (onset at 1000ms). On the basis of our results we can neither answer the question whether these oscillations may also be present in the absence of visual stimulation nor whether it might critically depend on the temporal sequence of the stimulus used. As far as we can tell, an oscillation in the delta band (3 Hz) correlating with properties of external stimuli has not been reported so far and its specific role remains to be further investigated.

Spectral analyses disclosed a second component which has not been reported so far in either human or monkey studies. This second component, arising from early visual cortex and oscillating in the alpha band, followed motion stimulus offset and showed a negative correlation with motion coherence. Alpha oscillations have struck scientists since the discovery of the EEG by Hans Berger in the late 20ies of the last century (Berger, 1929) and its properties and subclasses have been described extensively in many EEG and MEG studies (for review see: Pfurtscheller, 1996; Pfurtscheller, 1999; Klimesch, 1999a). Since the work of Berger it has been suggested that visual (or other sensory) task demands and visual attention in particular (e.g. Maruffo et al., 2001) are the primary factors that lead to a suppression of the alpha rhythm. This traditional view is obviously at odds with our finding of alpha synchronization emerging for the lower motion coherence levels. The reason is that the attentional load in our experiment – if at all – was highest in trials with low motion coherence because those were the most demanding. Moreover, one might expect a dependency of alpha power during motion presentation rather than after motion offset.

In order to resolve this seeming paradox we have to consider more recent work which indeed has prepared the ground for a paradigm shift in the current conception of alpha oscillations. In contrast to the earlier notion that alpha synchronization indexes ‘cortical idling’, i.e. a default resting state, it is becoming apparent that alpha oscillations indicate an active mechanism suppressing cortical activity that might interfere with task relevant signal processing (e.g.

Ward 2003). In line with this interpretation, recent studies have shown that alpha desynchronization is a local phenomenon which occurs specifically over task relevant cortical areas whereas task irrelevant regions show a pronounced synchronization (Klimesch et al., 1999b). This conclusion has been derived among others from studies directly testing alpha activity for different conditions of directed attention. For instance, Foxe et al. (1998) using an intermodal selective attention paradigm found that a visual cue indicating an upcoming auditory stimulus increased alpha activity over parieto-occipital cortex arguably reflecting disengagement of the visual attentional system. The opposite result, i.e. a decrease in occipital alpha power, was obtained when the cue announced a visual target. A later study of the same group (Fu et al., 2001) reported that this kind of occipital alpha modulation can also be induced by cross-modal (auditory) cues. Eventually, Worden et al. (2000) could demonstrate that spatial shifts of visual attention were paralleled by sustained focal increases of alpha synchronisation in a retinotopically specific manner: increases in alpha activity were seen only over occipital cortex contralateral to the direction of the to-be-ignored location. Taken together, these experiments suggest that alpha synchronization reflects active gating of uncued sensory modalities or spatial locations, respectively. The notion that alpha oscillations might indicate early inhibition of disturbing sensory input information as a part of the process of focusing attention on relevant information has been widened on the basis of studies not directly devoted to attention. For instance, Klimesch et al. (1999b) using a memory search paradigm described an increase in the alpha band with higher task difficulty over occipital cortex after the presentation of a set of letters which had to be memorized. Likewise, Jensen et al. (2002) reported a positive correlation between alpha band amplitude and memory load using a modified Sternberg task. Interestingly, these effects were restricted to the memory retention phase pointing to the possibility that alpha activation might play an important functional role by preventing any flow of disturbing information into areas retaining memory items. Based on their observations, Klimesch et al. (1999 b) suggested that alpha synchronization might in general reflect a mechanism which increases signal to noise ratios within the cortex by means of inhibition of unnecessary or conflicting processes to the task at hand. In other words, alpha synchronisation could indicate a more generalized inhibition of task irrelevant cortical areas.

In a similar way, occipital alpha activity increasing with lower motion coherence after motion offset seems ideally suited to protect the integration of visual motion signals in later areas from upcoming disturbing input. There is ample evidence that during the formation of a perceptual decision in a motion direction discrimination task, sensory evidence is integrated over time and accumulates until a critical threshold is reached - the weaker the sensory evidence the longer the integration will last (e.g. Snowden and Braddick, 1991, Britten et al., 1992, Patzwahl et al., 2000). Thus, with decreasing motion coherence the processing of motion direction information becomes not only more time consuming but also more sensitive to noise and therefore may benefit the more from gating mechanisms in early visual cortex impeding new signals from interfering with ongoing signal processing in higher-order areas such as area MT+. In line with the findings of Klimesch et al. (1999 b) or Jensen et al. (2002) this integration may include memorization of the stimulus seen.

As outlined earlier, the seeming paradox that alpha activity (assumed to reflect inactivation) may increase with task demand can be resolved only if one assumes that this activity is

spatially restricted. Indeed, the field distribution and source localization (see Fig. 4 and 5) revealed that the modulation of alpha oscillations was confined to early visual cortex whereas the global field power after test stimulus offset was still higher for coherent motion stimuli as compared to motion noise (Fig. 2a). This finding is in favour of the more specific interpretation that alpha oscillations might reflect an active gating mechanism implemented most of all - if not exclusively - in early sensory areas of the brain. Since neuromagnetic activity of primary visual cortex in our study did not depend on motion coherence during motion presentation we have to assume that the information on signal strength and, thus, on the need to enforce occipital gating, is not extracted by primary visual cortex itself but more likely is back-propagated from later specialized cortical areas such as area MT+ (Hupè et al. 1998).

Conclusions

In conclusion we could reveal two electrophysiological correlates of visual motion coherence in man using magnetoencephalography. A first MEG signal positively correlated with motion coherence during stimulus presentation could be attributed to extrastriate cortex including area MT+. The dependency of activity in human area MT+ on motion coherence reinforces the importance of this area in generating a percept of global motion and supports the notion that human and nonhuman primates share a similar visual motion system. A second MEG signal depending on motion coherence was an occipital oscillation in the alpha band whose amplitude decreased with motion strength after motion offset. We interpret this second signal as a reflection of an active gating mechanism which protects the ongoing processing of visual motion information in extrastriate cortical areas.

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2.2 Selective attention increases the dependency of cortical responses on visual motion coherence in man

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Introduction

Selective visual attention is a mechanism that improves perception by selecting which signals receive further processing: information which arises from a particular region in the visual field or which shares a particular feature is enhanced and deviating information is suppressed. Psychophysical studies have provided evidence for both mechanisms, the first one assigning preference to behaviorally relevant stimulus information ("signal enhancement") and the second one attenuating the disturbing impact of distractors ("noise reduction") (e.g. Posner 1980; Cave and Kosslyn 1989; Downing 1988; Lu and Dosher 1998; Yeshurun and Carrasco 1999). Likewise, functional imaging studies and single cell recordings have demonstrated that neural responses to attended visual stimuli are enhanced relative to the same stimuli when unattended (e.g., Corbetta et al. 1990; Moran and Desimone 1985; Treue and Maunsell 1996) and that neural responses to unattended stimuli are attenuated when vision is engaged elsewhere (Rees et al. 1997; for reviews see Kastner and Pinsk 2004; Reynolds and Chelazzi 2004; Treue and Martinez-Trujillo 2006).

A direct correspondence between psychophysical and neurophysiological measures has been carefully established by studies in awake behaving monkeys (e.g. Newsome et al. 1998; Britten et al. 1992; Cook and Maunsell 2002). Requiring the monkey to extract a global motion signal embedded in noise by varying the signal-to-noise ratio, i.e. the percentage of coherently moving elements, psychometric and "neurometric" functions could be compared in a quantitative manner. Following this approach, numerous studies have revealed positive, approximately linear correlations between motion coherence and firing rate such as observed in area MT/V5 (Britten et al. 1992; Newsome et al. 1989; Britten et al. 1996) or area LIP (Shadlen et al. 1996, 2001; Gold and Shadlen 2003; Roitman and Shadlen 2002). This correspondence reflects the simple rule that the discrimination of visual motion as predicted on the basis of neuronal responses of visual cortex will be better the more, the stronger and more reliably the responses would depend on motion coherence.

The goal of the present study was to test whether selective attention changes the dependency between cortical responses and motion coherence in accordance with its influences on perception. To this end, we resorted to a motion discrimination paradigm for which we recently observed a strong positive correlation between visual motion coherence and evoked neuromagnetic responses in man (Händel et al. 2007). Specifically, the MEG response examined was a low-frequency (3 Hz) oscillation, phase locked to stimulation and originating from contralateral extrastriate cortex (Händel et al. 2007). Similar to BOLD responses recorded from human extrastriate areas (MT+, V2, V3a: Rees et al. 2000; V3a: Braddick et al. 2001) or high-frequency oscillations (Siegel et al. 2007), the amplitude of this response reflects a key feature of motion-sensitive visual neurons, namely their coherence dependency, and was taken here as a compound measure of population responses in human extrastriate

cortex. We report that selective attention has a profound influence on the coherence dependency of this oscillation, suggesting changes in the signal-to-noise ratio at the neural population level as predicted by single cell recordings (Martinez-Trujillo and Treue 2004).

Materials and Methods

Seven healthy subjects, 2 males and 5 females with a mean age of 24 +/- 3 years participated in this study. All subjects had normal or corrected to normal vision. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the guidelines of the local ethics committee of the faculty of medicine of the University of Tübingen, which approved the study.

Psychophysical task and eye movement control: Subjects were seated upright in a magnetically shielded room (Vakuum- Schmelze, Hanau, Germany) and were instructed to sit as motionless as possible during the MEG recording. Stable posture was supported by a chinrest attached to the MEG chair. The computer-generated visual stimuli were rear projected onto a large translucent screen (DLP-projector, frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 92 cm in the magnetically shielded room. Viewing was binocular.

The visual stimulus consisted of 6 periods, each lasting 500ms (see Fig.1). After a first fixation period (central fixation dot, diameter 10 arcmin) an arrow instructed subjects to covertly shift attention either into the left or the right hemifield. The attentional cue was followed by two random dot kinematograms (RDKs) each of which covered a square of 16 x 16 deg and was centred 15 deg right and left, respectively, of the fixation point. RDKs consisted of 1500 white squares (side length = 8 arcmin, lifetime = 1000ms, dot density ~ 6dots/deg2, luminance 47cd/m2) all moving incoherently, i.e. in all possible directions with a resolution of 1 degree, at a common speed of 6deg/s. After the presentation of this first pair of RDKs ("prestimulus"), a second pair of RDKs, the "test stimulus", started. The properties of the test stimulus were identical to those described for the prestimulus except that a certain percentage of the dot elements moved coherently in the same direction (either to the left or to the right). Specifically, the percentage of coherently moving dots was either 5%, 20%, 50%, or 100% of all dots in an individual trial. While the amount of motion coherence was always identical for the two RDKs in a given trial, global motion direction could be the same or different as randomly chosen by the computer. After a subsequent second fixation period, a second arrow indicated for which of the two RDKs subjects had to indicate the direction of coherent motion (two-alternative forced-choice). Valid cueing as defined by congruent orientation of the attentional and the instructional cue was applied in 80% of trials. Trials with a valid cue could either show predefined motion coherence (4 levels, 120 presentations each) or motion coherence varied according to an adaptive staircase procedure. Invalid cued trials showed only adaptive coherence levels. Only the valid trials with predefined motion coherence served the collection of neuromagnetic responses and were presented randomly interleaved with trials whose motion coherence was varied according to an adaptive staircase procedure in order to determine two psychophysical thresholds, one for the condition of valid cueing and a second one for the condition of invalid cueing. In order to assess the ability to discriminate the motion direction embedded in noise, the percentage of correct responses was plotted as function of motion coherence and fitted by a probit function. The perceptual

threshold was defined by the coherence level for which the probit function predicted 75% correct responses. In order to correlate perceptual discrimination with the electrophysiological responses obtained for the four coherence levels, the proportion of correct responses was derived also for these levels based on the same probit approximation and compared by T-statistic.

During all experiments, eye movements were monitored using a homemade video system taking the pupil's center as measure of eye position. Recordings were stored at a sampling rate of 50 Hz and analyzed offline in order to assess the quality of fixation. In particular, the influence of spatial orienting on the following oculomotor parameters was tested for the period of test stimulus presentation, i.e. slow eye drifts (eye velocity), deviations from the fixation point (eye position), and the number and amplitude of saccades. To this end, the means of the various oculomotor measures were calculated in each subject for the epoch of the test stimulus and compared between the two possible directions of the attentional cue by means of a paired T-test.

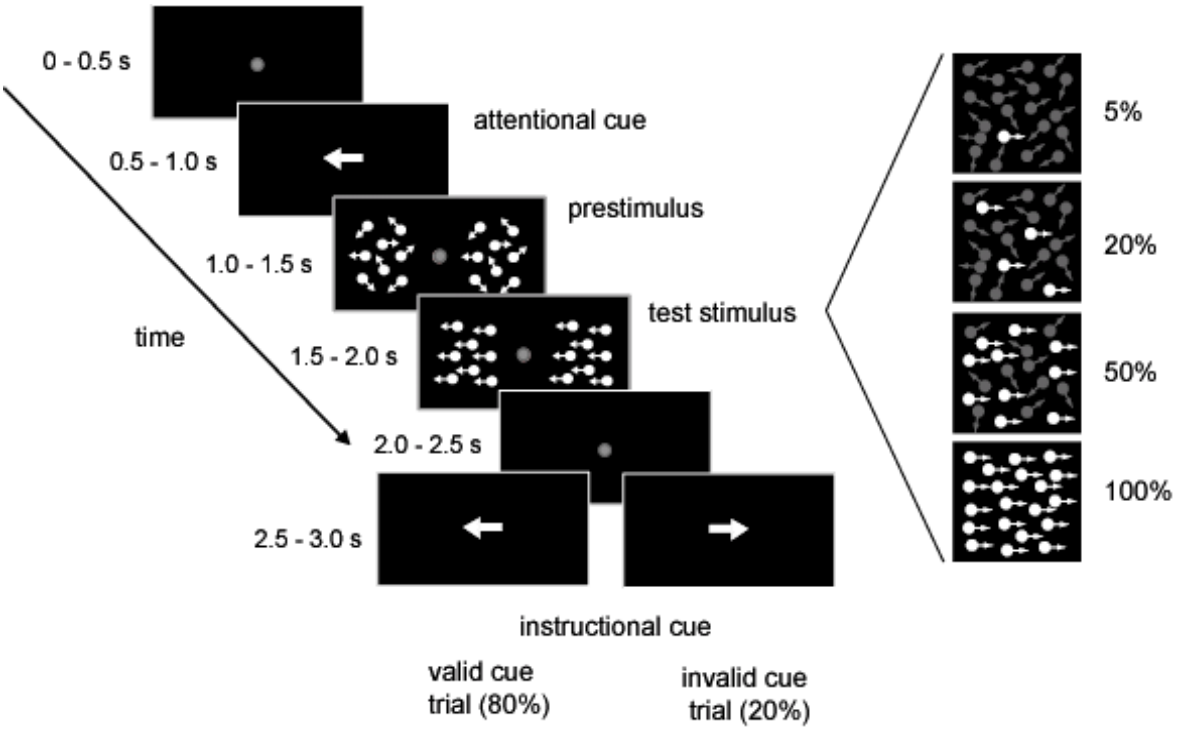

Figure 1) Experimental paradigm. The stimulus consisted of 6 periods each lasting 0.5s. After a first fixation period an arrow instructed subjects to shift their attention either to the left or to the right. The first motion stimulus comprised two random dot kinematograms (RDKs) consisting of incoherent motion. The following test stimulus involved presentation of coherent motion defined by the percentage of dots moving in the same direction (5%, 20%, 50%, or 100%, stimulus schemata are shown on the right side). Global motion direction was either to the left or to the right and could be different for the two RDKs. After a subsequent second fixation period, a second arrow indicated for which of the two RDKs subjects had to indicate the direction of coherent motion (two-alternative forced-choice). Valid cueing as shown in this example was applied in 80% of trials. Trials with predefined motion coherence (120 presentations each) served the collection of neuromagnetic responses and were presented randomly interleaved with trials whose motion coherence was varied according to an adaptive staircase procedure in order to determine the psychophysical thresholds.

Recording and analysis of the MEG signals: Neuromagnetic activity was recorded using a whole-head MEG system (CTF Inc., Vancouver, Canada) comprising 151 first-order magnetic gradiometers. The signals were sampled at a rate of 625 Hz. Recording epochs lasted from stimulus onset to arrow offset plus 200ms, leaving 3200ms of recording time for each trial. Spectral analysis was performed as follows. The recordings were first of all baseline (450 - 500ms) corrected, Gaussian filtered (3 Hz +/-2 Hz) for each trial and channel, and subjected to a Hilbert transformation in order to extract the spectral amplitude which had been found previously to depend on motion coherence (Händel et al., 2007). Next, dependencies on motion coherence were tested for two separate datasets defined by the direction of spatial orienting in the given trial (to the right or to the left, respectively). To this end, for both conditions the 3 Hz amplitudes were averaged in each subject across the corresponding trials for each of the 4 different coherence levels, separately. The influence of motion coherence (5%, 20%, 50%, and 100%) on the spectral amplitudes was then assessed for both conditions by a one-way repeated measures ANOVA performed on all trials of the 7 subjects and for each channel (n=150; one sensor was excluded because of malfunction). This analysis was performed for 6 separate time periods, breaking up the time from prestimulus onset to the end of the second fixation period into periods of 250 ms. Sensors were considered to be significant if two neighbouring sensors showed a p-value below 0.05 in a given time period. Amplitudes of significant sensors were further compared by means of a three-way ANOVA with repeated measures with the factors motion coherence, hemisphere (location of sensors, either left or right) and sensor location relative to the attended hemifield.

Results

Behavioral Results: Subjects shifted attention according to cue information as indicated by the fact that valid cueing resulted in perceptual thresholds of 19.9% (percentage of coherently moving dots required to obtain 75% correct responses) as opposed to 42.3% in trials with invalid cueing (t-test, $p<0.01$, Fig 2A). The strongest differences in perceptual discrimination were observed for intermediate coherence levels, i.e. for the 20% and 50% motion coherence stimuli (Fig. 2B). Specifically, group differences for the proportion of correct judgements were negligible for the 5% and 100% stimuli but amounted to 22.2% (20% coherence, t-test: $p<0.005$, corrected for multiple comparisons) and 15.2% (50% coherence, not significant) for the other levels. As can be derived from Fig. 2B, due to attentional instruction the behavioral performance at the 20% level with attention was very similar to the one possible without attention at the 50% level. Importantly, the perceptual modulation observed was not attributable to eye movements since all oculomotor parameters considered, i.e. eye velocity, eye position and number and amplitude of saccades during presentation of the test stimulus, showed no significant difference between trials differing with respect to the direction of cueing (either to the left or to the right; paired t-test, $p>0.05$ corrected for multiple comparisons). For instance, changes in horizontal eye position induced by the attentional cue were small amounting on average to only 0.4° (attention directed to the right: +0.7°+/-0.3 [means and STD]; attention directed to the left: +0.3°+/-0.3 [means and STD]).

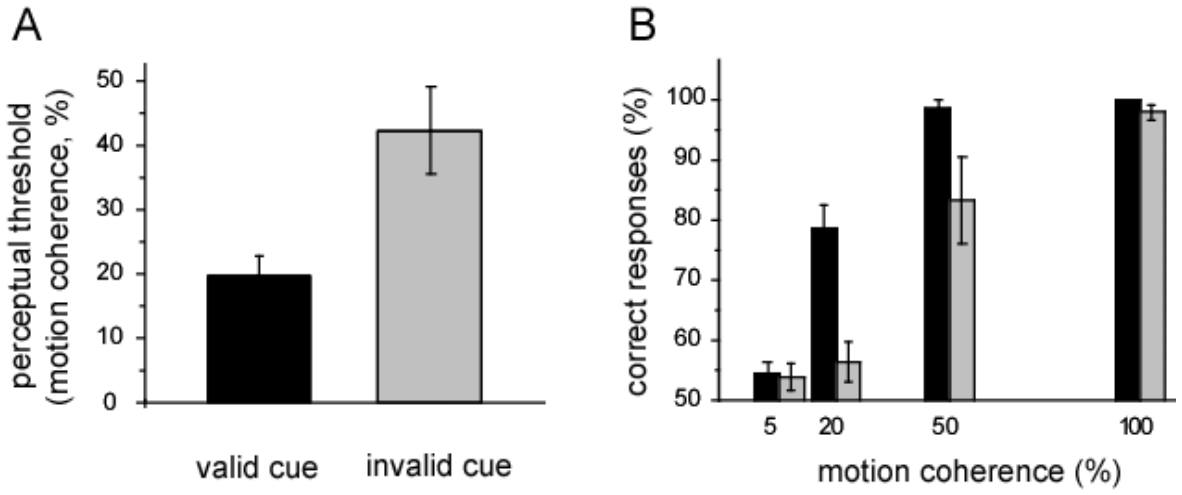

Figure 2) Behavioral results. **A** The perceptual thresholds (group means +/- S.E.M.) for valid and invali cueing. **B** The proportion of correct judgements for direction of motion plotted for those coherence levels f which MEG responses were collected (group means +/- S.E.M).

Neuromagnetic responses: As outlined in the Methods section, cortical responses were recorded during the task using whole-head magnetoencephalography and analyzed off-line in order to search for dependencies on motion coherence and selective attention. Since our previous work had demonstrated a strong modulation of a 3Hz oscillation by motion coherence the present analysis was focused on spectral amplitudes in a bandwidth of 3 (+/-2) Hz (Händel et al., 2007). Corroborating our earlier finding, significant influences of motion coherence were strongest during the second half of test stimulus presentation (250-500 ms after test stimulus onset). As shown in Fig.3B, which plots the grand averages, i.e. averages over all subjects and all sensors, of the gaussian filtered signal for the different coherence levels as function of time, this dependency was not strictly monotonic. The reason is that the amplitudes evoked by the 5% coherence stimulus were slightly higher relative to the 20% response thus deviating from the overall increase observed for higher coherence levels.

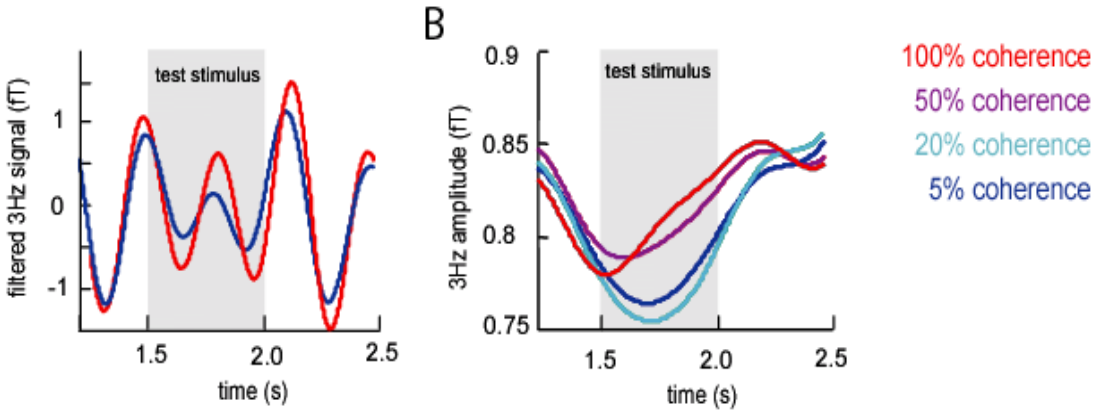

Figure 3) A Time course of the Gaussian filtered (3Hz+/-2Hz) MEG responses averaged over all sensors of one hemisphere in one exemplary subject (red: 100% coherence, blue: 5% coherence). The difference between curves depicts the dependency of the oscillation on motion coherence with larger amplitudes for higher coherence levels. **B** Group data: Time course of the oscillation after amplitude demodulation (average over all sensors and subjects).

In order not to disregard nonmonotonic dependencies, we performed an analysis of variance not postulating a particular mathematical relationship. Specifically, dependencies on motion coherence and selective attention were tested by subjecting the spectral amplitudes to a one-way repeated measures-ANOVA with the factor motion coherence (4 levels) for the two directions of spatial orienting (to the left or to the right), separately. As shown in Fig.4A statistically significant dependencies on motion coherence were confined to sensors lying contralateral to the attended RDK but were absent for ipsilateral sensors. The fact that these dependencies emphasized temporo-occipital sensors under both conditions was consistent with our earlier study (Händel et al., 2007) suggesting human area MT+ and neighboring cortex as the underlying sources.

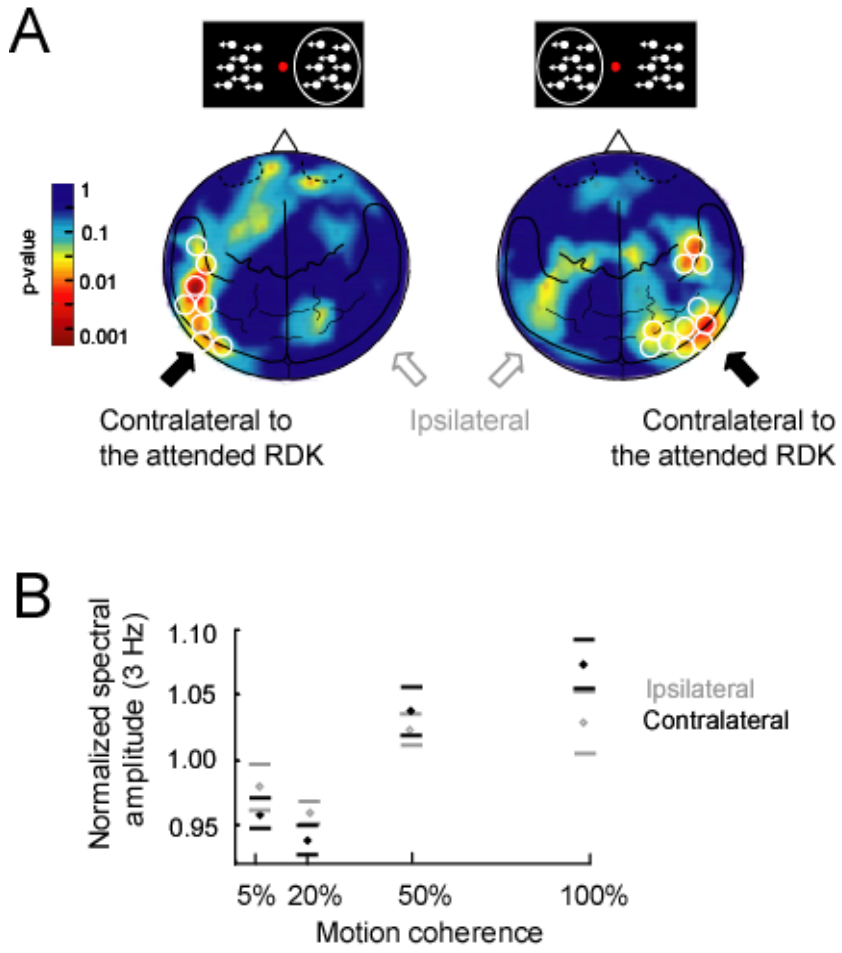

Figure 4) A Statistical probability mapping of spectral amplitude dependencies on motion coherence projected onto two-dimensional MEG sensor maps (seen from above, nose up). P-values denoting the level of statistical significance of the effect of motion coherence on spectral amplitude present during the second half of test stimulus presentation (250-500ms after test stimulus onset). P-values were calculated from an ANOVA (see Methods) and are color-coded here in order to provide a quasi-field distribution. Distributions of p-values are shown for the two directions of spatial orienting indicated by the white elipses surrounding one of the RDKs in the sketches of stimuli. Note that the motion coherence of the visual stimulus was always the same covering corresponding parts of both visual hemifields and that only the attentional instruction and possibly motion direction was different. The white circles mark those sensors which revealed a significant dependency on motion coherence (two adjacent sensors with $p<0.05$). **B** Normalized spectral amplitudes obtained from the significant sensors marked in A (means and S.E.M. of both the left and right marked sensors) as a function of motion coherence shown separately for sensors lying contralateral (black) and ipsilateral (grey) to the attended RDK. Since sensors over the left and right hemisphere (independent of the attentional state) showed no significant difference in coherence modulation (three-way ANOVA), responses from sensors over both hemispheres were pooled and stratified according to sensor location relative to the attended hemifield (either ipsi- or contralateral). Normalization was performed on single subject and sensor basis by averaging amplitudes across the two directions of spatial orienting and all coherence levels.

In order to capture the modulation of the oscillation in more detail, spectral amplitudes were extracted from those sensors that exhibited a significant influence of motion coherence under

either of the two directions of spatial orienting. As can be drawn from Fig.4B the main effect of spatial orienting was an increase in coherence modulation of spectral amplitudes.
An overall difference, however, between amplitudes derived from sensors lying ipsilateral to the attended hemifield as compared to amplitudes of contralateral sensors was not present (three-way repeated measures ANOVA with the factors motion coherence, sensor location [left or right] and sensor location relative to the attended hemifield [ipsilateral or contralateral]; motion coherence: $p<0.001$; sensor location relative to the attended hemifield: $p=0.37$; interaction: $p<0.001$). On average, amplitudes picked up from the right cortical hemisphere were significantly higher as compared to left hemisphere responses (three-way ANOVA; influence of sensor location, $p<0.01$), however, the interaction with neither motion coherence ($p=0.9$) nor sensor location relative to the attended hemifield ($p=0.36$) was significant. Post-hoc analyses (paired t-tests) revealed significant differences for all coherence levels except the 50% stimulus with attention resulting in higher amplitudes for stimuli with high global net motion (100% coherence: $p<0.001$) and lower amplitudes for stimuli dominated by noise (5% coherence: $p=0.002$; 20% coherence: $p=0.0048$).

Discussion

Cortical oscillations like the 3Hz signal tracked here using MEG are thought to reflect synaptic potentials and other slow electric signals such as spike afterpotentials and voltage-dependent membrane oscillations largely determined by functional states of cortex and thalamus. As a rule, slower frequencies are thought to involve spatially more extensive synchronous activation of a large neuronal pool (Buszáki 2006). We therefore set out to take this oscillation as a compound measure of population activity of human cerebral cortex and asked whether this measure would show signal-to-noise features correlating with the perceptual changes induced by selective attention. This attempt was motivated by the fact that the spectral amplitudes of this oscillation had shown a robust, monotonic dependency on motion coherence in a previous study (Händel et al. 2007).
A clear dependency on motion coherence was replicated in the present study, although the relationship was nonmonotonic due to the small increase of spectral amplitudes at 5% compared to 20% motion coherence, the former level not tested previously. Similar increases at low coherence levels have been reported by Rees et al. (2000) using functional magnetic resonance imaging. The authors reported a linear relationship between BOLD responses and motion coherence in areas MT+, V2, and other visual areas but found second-order correlations in the middle occipital gyrus and area V3a. The relationship observed here may therefore reflect a weighted average of contributions from different cortical areas not disentangled by MEG. In principle, emphasis of the responses modulated by motion coherence on temporo-occipital cortex is in line with area MT+ and neighboring cortex as the underlying source. Any attempt to provide a more detailed spatial description of the generators, however, seems complicated given the fact that up to 17 (!) motion sensitive cortical regions have been established in the human brain (Sunaert et al. 1999).
The non-linearity of the dependency notwithstanding, we may ask whether the oscillation changed in a way corresponding to the perceptual differences induced by selective attention. Specifically, if the 3Hz oscillation were indeed a reflection of compound activity giving rise to the altered discriminational performance its amplitude should meet the following

predictions: First, as argued in the Introduction, an improvement in motion perception should be indicated by an increase of coherence dependency. Second, amplitudes for a given coherence level should be higher with attention provided that the perceptual performance would be improved relative to the same level when unattended. Third, along the line of arguments put forward by Cook and Maunsell (2002), behavioral performance should follow changes in neuronal responses, whether those arise from stimulus differences or changes in behavioral state. In other words, the neuronal responses should be more or less constant for conditions that were the same in behavioral terms, even if the stimulus features were different. Our results are clearly in accordance with the first prediction: the main effect of misdirected selective attention was a striking loss of coherence dependency. However, the other two predictions are violated. Quite contrary to the second one, the amplitudes obtained for the coherence level with the strongest perceptual differences (the 20% motion coherence level, see Fig. 2B) were smaller with attention as compared to without attention (Fig. 4B). Likewise, amplitudes for similar behavioral performances were by no means constant as exemplified by the responses obtained at 20% and 50% motion coherence. The behavioral performance at the 20% level with attention was virtually the same as the one possible without attention at the 50% level (Fig. 2B). The spectral amplitudes of this pair of conditions, however, were quite different (Fig. 4B). The interpretation that the modulation of the neuromagnetic response induced by attention reflects the change in percept, therefore, seems only partially supported at first glance. Likewise, our differential effect of selective attention depending on motion coherence seems to be in conflict with a carefully performed single cell recording study showing response enhancement by attention not only for coherent motion but even for motion stimuli lacking any coherence (Cook and Maunsell 2002).

In order to come up with an explanation for this seemingly conflicting pattern of results it is important to note that the MEG signal analyzed here represents a compound measure of responses to both coherent and incoherent motion with the latter comprising visual motion in all possible directions. In fact, a major difference between this human study and previous monkey experiments is that only in the animal it is possible to adjust the stimuli to the preferences of the neuron under study. However, by matching stimuli to the preferred directions of the neuron (Cook and Maunsell 2002) the influence of selective attention on motion coherence has only been examined for a particular selection of cells. On the other hand, the coherence modulation of neurons with deviant preferences has not been tested but might nevertheless contribute to the attentional effect (Martinez-Trujillo and Treue 2004). We suggest that the change in coherence dependency observed here is a reflection of all the neurons exhibiting any motion preference and that the responses to coherent and incoherent motion, respectively, might be differentially modulated by selective attention. Accordingly, the increase in spectral amplitude observed here at 100% motion coherence would reflect response (signal) enhancement such as reported by many studies (e.g. Treue and Maunsell 1996; Cook and Maunsell 2002). On the other hand, the decrease at low coherence levels (20%, 5%) would indicate noise reduction outweighing enhancement of the response to a weak coherence signal. For this interpretation to be valid, knowledge on how to disentangle signal (coherent motion) from noise (incoherent motion) must be available. Indeed, in our paradigm such knowledge was offered by the fact that coherent motion always occurred in horizontal direction. Importantly, attention based on motion direction has been demonstrated

in single cell recordings to differentially modify neural response rates: those neurons with a preference close to the attended feature are going to experience an enhanced response gain but others for which the attended feature is different from the neuron's preference will be reduced in their firing rate (Martinez-Trujillo and Treue 2004; Treue and Martinez-Trujillo 2006). In this way, the present observation of a differential change in neural response depending on motion coherence is fully in line with the concept of a push-pull effect across the population as suggested from single cell recordings.

Conclusions

In summary, we tested the effects of selective attention on MEG responses in man picked up from extrastriate cortex and correlating with motion coherence. The paradigm applied carefully controlled for parameters unrelated to selective attention such as alertness or eye movements. The modulation of motion perception induced by selective attention was paralleled by changes in coherence dependency of the MEG response. Specifically, attention directed to a given hemifield increased and decreased the coherence modulation of the MEG response over contralateral and ipsilateral visual cortex, respectively, indicating a change in the neuronal signal-to-noise ratio at the population level.

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2.3 Deficits in visual motion perception due to cerebellar lesions are paralleled by changes in motion coherence specific cortical response modulation

Introduction

Unlike the cerebrum the cerebellum is mainly viewed as irresponsible for any particular overt behavior or psychological process but is rather seen as a computing machine which supports the rest of the brain by modulating cortical activity (Bower and Parsons, 2003). Such a supporting function is already indicated by the uniform architecture of the cerebellum as pointed out by Ramnani (2006). If the support provided by the cerebellum is insufficient a cortical dysfunction will result. After a long standing debate it is today widely accepted that the cerebellar influence can affect motor as well as non-motor processes visible in various impairments after cerebellar lesions (for discussion see Schmahmann, 1998; Glickstein, 2006; Daum and Ackerman, 1995). The strongest argument in favor of this view is the anatomical connection between the cerebellum and motor cortex as well as cortical non-motor areas. Specifically, it has been shown that information from motor, premotor, posterior parietal, cingulate, and prefrontal cortex is transmitted to the cerebellar cortex via corticopontocerebellar pathways (Brodal, 1978; Glickstein et al., 1985; Schmahmann and Pandya, 1997) and that the cerebellum in turn also projects not only to primary motor cortex but also to premotor, oculomotor, prefrontal, and posterior parietal cortical areas (Lynch et al., 1994; Middleton and Strick, 1994; 2001; Hoover and Strick, 1999; Clower et al., 2001). Even more, the cerebellum and the cerebrum seem to form multiple closed-loop circuits (Kelly, 2003, for overview see also Ramnani, 2006).

Interestingly, even though the cerebellar-cortical connections have been shown for quite some years, the actual influence of the cerebellum on cortical activity is not known and only vaguely discerned by crossed cerebellocerebral diaschisis (CCCD) which describes a general decrease of cortical activity contralateral to cerebellar lesions (Komaba, 2000; Broich, 1987). The aim of this study was to show that cerebellar lesions can cause defined activity changes in specific cortical areas indicated by deficits visible in psychophysical tests. Cortical activity responsible for the faculty tested should be altered by missing cerebellar input and correlate with the specific psychophysical deficiency. Unfortunately, many of the non-motor processes claimed to be influenced by cerebellar activity are still heavily under debate due to contradictory psychophysical results (for discussion see Schmahmann, 1998; Glickstein, 2006; Daum and Ackerman, 1995). In the study at hand motion perception was investigated which has been reported to be deficient in patients with cerebellar lesions by various independent groups (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier et al., 1999; Jockisch et al., 2005). This perceptual impairment manifests itself in such a way that in a random dot display more dots have to move coherently in one direction in order to enable patients to detect the prevalent global motion direction.

If the cerebellum indeed influences the activity of those cortical regions which process such motion stimuli one can generate a concrete prediction of what part of the cortex should be affected. Considering the nature of the deficit investigated, area MT, first described by Allman and Kaas (1971) and Dubner and Zeki (1971), is a very likely candidate region for cerebellar influence. First of all complex motion, like motion embedded in noise, is most

likely processed in area MT with its large receptive fields (Desimone and Ungerleider, 1986) and extremely high percentage of motion direction selective neurons (Maunsell and van Essen, 1983). A second striking observation is that the perceptual deficit in cerebellar patients resembles very much the one observed in MT lesioned human (Vaina et al., 2001) and non-human primates (Pasternak and Merigan, 1994; Newsome and Park, 1988). Third, the stimulus parameter which affects the percept in cerebellar patients (i.e. motion coherence) is depicted in most MT neurons since they exhibit an increased firing rate with rising motion coherence (Britten et al., 1992; Newsome et al., 1989; Britten et al., 1996). The same relationship could be found for human area MT+ (a complex of various extrastriate areas including area MT) using various imaging techniques (fMRI: Rees et al., 2000; Braddick et al., 2001; MEG: Aspell et al., 2005: Maruyama et al., 2002; Händel et al., 2007).
We took advantage of the knowledge that MT+ activity would manifest itself in a coherence dependency in order to localize these motion processing areas. A possible influence of the cerebellum on these areas could then be investigated. Magnetoencephalography (MEG) was used, a method well capable to pick up activity from area MT+ in humans (Lam et al., 2000; Maruyama et al., 2002; Händel et al., 2007) but still able to resolve the precise timing structure of any magnetic response. Using a random dot display with changing motion coherence levels impaired motion perception could be demonstrated in cerebellar patients which was paralleled by changes in occipito-temporal activity.

Materials and methods

Subjects: Eight patients (4 females, mean age 38 +/- 8 years, range: 26 - 50) and thirteen age matched healthy controls (8 females, mean age 36 +/-11 years, range 23 - 58) participated in this study. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the guidelines of the local ethics committee of the medical faculty of the University of Tübingen, which approved the study. All subjects had normal or corrected to normal vision, controls had no history of neurological disease. The patient group included only those with lesions/ degeneration restricted to the cerebellum. Three patients had an idiopathic cerebellar ataxia (IDCA) which is thought to constitute forms of "pure cerebellar ataxia" (Manto and Pandolfo, 2002). In two patients parts of the cerebellar hemispheres were removed in the course of tumor treatment and four patients had suffered a posterior inferior cerebellar artery (PICA) insult at least 3 month before the experiment also showing distinct cerebellar damage. Since magnetoencephalography is extremely sensitive to muscle activity it was made sure to only include cerebellar patients who, besides exhibiting normal eye movements, showed no signs of tremor.
Procedure and stimulus material: Subjects were seated upright in a magnetically shielded room (Vakuum- Schmelze, Hanau, Germany) and were instructed to sit as motionless as possible during the MEG recording. Stable posture was supported by a chinrest attached to the MEG chair. The computer generated visual stimuli were rear projected onto a large translucent screen (DLP-projector, frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 92 cm in the magnetically shielded room. Viewing was binocular.
The visual stimulus consisted of 5 periods (see Fig.1) each being observed by the subjects during controlled stationary fixation. During the first 500 ms, only a stationary red dot (diameter 10 arcmin) was presented in the middle of the screen which served as the fixation

target and which remained visible for a total of 2 s. The first 500 ms period was followed by a second one introducing a random dot kinematogram (RDK) which covered a square of 16 x 16 deg and was centered 15 deg right of the fixation point. The RDK consisted of 1500 white squares (side length = 8 arcmin, lifetime = 1000 ms, dot density ~ 6dots/deg2, luminance 47cd/m2) all moving incoherently, i.e. in all possible directions with a resolution of 1deg, at a common speed of 6deg/s. After the presentation of this first RDK that will also be refered to as the "prestimulus", a second RDK, the "test stimulus", started. The properties of this second RDK were identical to those described for the prestimulus except that it lasted only 200 ms and that a certain amount of dot elements moved coherently in the same direction (either to the left or to the right). Specifically, the percentage of coherently moving dots was either 0%, 20%, 40%, 60%, 80%, or 100% of all dots in the individual trial. After a subsequent second fixation period (500 ms), an arrow was presented in the middle of the screen pointing either to the left or to the right side as randomly chosen by the stimulus generator. Subjects were instructed to keep fixation as accurately as possible during the whole trial and to indicate by lifting their right or left index finger whether the motion direction of the dots of the test stimulus was identical (right index finger) or opposite (left index finger) to the pointing direction of the arrow. Note that the motor response could not be planned until the arrow had been presented, thus, guaranteeing that the MEG signals during the first 700 ms after test stimulus onset were not related to movement preparation. The individual measurement consisted of 720 single trials with each coherence level (n=6) being presented 120 times in a randomized sequence. In order to assess the ability to discriminate the motion direction embedded in noise, the percentage of correct responses in the individual measurement was plotted as function of motion coherence and fitted by a probit function (McKee et al., 1985). The perceptual threshold was defined by the coherence level for which the probit function predicted 75% correct responses.

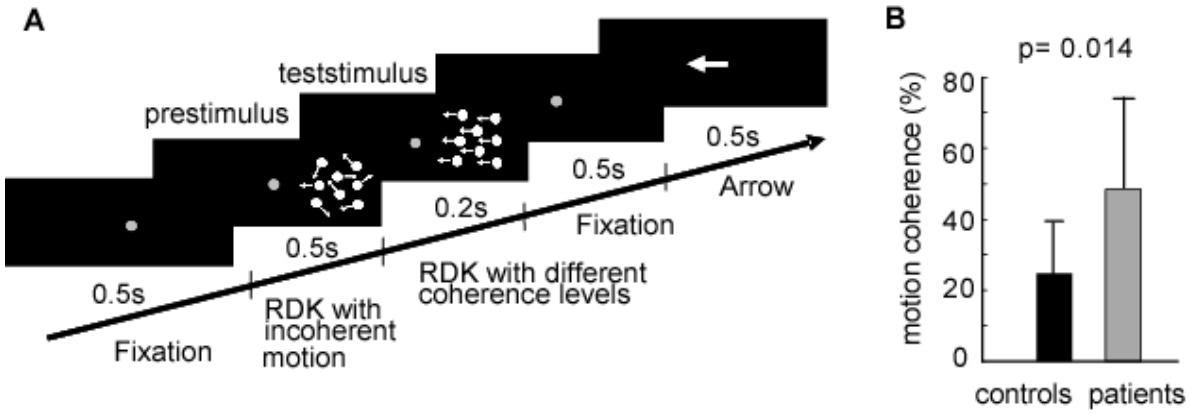

Figure 1) Time course of the stimulus and the perceptual thresholds A) The stimulus consisted of 5 periods each lasting 500 ms except the presentation of the coherent motion which lasted only 200 ms. In contrast to the "prestimulus", a random dot kinematogram (RDK) consisting of incoherent motion, the following "test stimulus" involved the presentation of coherent motion the percentage of which was varied between 0% and 100% in steps of 20%. The coherent motion signal was moving either to the left or to the right. Subjects had to indicate whether the motion direction of the coherently moving dots of the test stimulus was identical or opposite to the pointing direction of the arrow presented at the end of the trial. B) The average perceptual threshold for patients (48.4, +/- 25.6 STD, grey bar, n=8) compared to the control group (24.5, +/- 14.7 STD, black bar, n=13) showing a significantly (T-test, p=0.014) higher motion coherence threshold in patients.

During all experiments, eye movements were monitored using a homemade video system taking the pupil's center as measure of eye position. Recordings were stored at a sampling rate of 50 Hz and analyzed offline in order to assess the quality of fixation. Oculomotor parameters was determined, i.e. slow eye drifts (eye velocity), deviations from the fixation point (eye position) and the number and amplitude of saccades, and the means of these measures were tested for differences between patients and controls by means of a T-test. For 2 patients who temporally failed to maintain fixation, data was re-examined and all trials were excluded from the MEG analysis that exceeded a deviation of 2 deg in the x-axis from the fixation spot. At least 60 trials for each coherence level were still valid with respect to our criterion the MEG-analysis was conducted using this reduced number of trials. Since no unexpected signal development could be observed in these patients this trial number was considered as sufficient and all further analysis was conducted on 8 patients. For one patient eye movement recordings were not available due to technical problems, however, fixation was controlled online visually during the recording.

Recording and analysis of the MEG signals: Neuromagnetic activity was recorded using a whole-head MEG system (CTF Inc., Vancouver, Canada) comprising 151 first-order magnetic gradiometers. The signals were sampled at a rate of 625 Hz. Recording epochs lasted from stimulus onset to arrow offset plus 500 ms, leaving 2700 ms of recording time for each trial. The subject's head position was determined at the beginning and at the end of each recording by means of localization coils fixed to the nasion and preauricular positions to ensure that head movements did not exceed channel separation. MEG recordings were baseline corrected with respect to the last 100 ms of the first interval of fixation preceding the presentation of the first RDK. Trials contaminated by muscle activation or other artifacts defined by activity surpassing 3 times the normal MEG amplitude were excluded.

In order to test for a general difference in activation strength between patients and controls independent of the coherence level the average MEG response over all coherence levels was compared between groups. Specifically, the root of the mean squared magnetic fields (RMS) was calculated for each subject, each sensor and each sample separately. RMS values were averaged over sensors resulting in the time course of the global field power (GFP). Further the mean was calculated over 500 ms for all stimulus periods except the test stimulus, which lasted only 200 ms, and a T-test was applied for each time period.

In a second step the influence of motion coherence on cortical activity was analyzed for the two groups separately. Since it has been shown previously that there is a linear increase in brain activity with increasing motion coherence (Händel et al., 2007) a (running) linear regression between the coherence level and the GFP (now calculated separately for the six coherence levels) was conducted for each point in time, separately for the group of patients and controls. This analysis disclosed the time course of influence on brain activity by motion coherence. The strength of this influence is given by the steepness of the regression which is expressed in the beta-values and significance is indicated by the obtained p-values. GFP within 10 ms (6 samples) around the first time point p-values fell below 0.05 were compared between groups for each coherence level separately by means of a T-test and resulting p-values were corrected for multiple comparisons.

Since one possible feature of patient data is a greater variability in latency group analysis was abandoned and a correlation analysis was conducted for all subjects separately. Specifically, a

running linear regression between the GFP and the coherence levels (6) for a time bin of 6 consecutive samples was calculated for each subject. The time bin was shifted (in steps of 6 samples) from 150 to 600 ms after test stimulus onset and the maximal beta-value within this time period and the corresponding latency were extracted for each individual. The maximal beta values of all subjects had a corresponding p-value of $p < 0.001$. In order to investigate if the individual ability to perceive coherent motion was connected to the strength of coherence dependent activity modulation (retained in the beta-values) the individual perceptual threshold was correlated with the maximal beta value and its latency, respectively, by means of a linear regression.

Finally, in order to pin down the localization of the brain activity modulated by motion coherence again a running linear regression over coherence levels for the two groups was conducted (patients and controls, respectively) but now for RMS values of each sensor separately. Specifically, the absolute values were averaged over trials providing the positive time course of activity for each sensor and coherence level. Samples within a 50 ms time bin were further averaged and a linear regression over the group data was conducted. The time bin was shifted from 100 ms to 600 ms after test stimulus onset in steps of 50 ms. Beta and p-values for each sensor over time (with a resolution of 50 ms) were obtained for each group and beta values were plotted as a quasi field distribution. All analysis was calculated using MATLAB (version 6.5.1).

Results

Corroborating earlier reports on perceptual deficits in cerebellar patients (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier et al. 1999; Jockisch et al., 2005) the present study showed a significantly decreased (T-test, $p=0.014$) perceptual threshold in patients (average: 48.4, +/- 25.6 STD, grey bar) compared to a healthy control group (average: 24.5, +/- 14.7 STD, black bar). Perceptual thresholds (75% correct responses) plotted in Fig. 1B show that patients needed significantly higher motion coherence in order to correctly identify the global motion direction within a RDK.

In order to explore if this perceptual difference is paralleled by changes in brain activity the overall magnetic brain response was compared between groups. The time course of the GFP (magnetic activity averaged over all trials and all sensors) can be seen for patients and controls in Fig. 2A. A first peak at around 650 ms after stimulus onset, most probably reflecting the incoherent motion onset and the consequential luminance change, was prevalent for both groups likewise with congruent response strength. A second increase in magnetic activity starting at around 150 ms after test stimulus onset could also be observed for patients and controls similarly and responses stayed overlapped until about 100 ms after arrow presentation onset. From here on magnetic activity within the control group surpassed the one in the patient group. In order to obtain a statistical criterion, the averaged response was compared between groups within each stimulus period. Testing all stimulus periods separately, only the time period between 1700 ms to 2200 ms, namely the period of arrow presentation showed a significant difference between groups (T-test, $p=0.0015$). The field distribution of activity for this time period, plotted in Fig. 2B, indicates that activity was focused on the occipito-temporal cortex contralateral to the stimulation and on ipsilateral occipital sensors close to the midline.

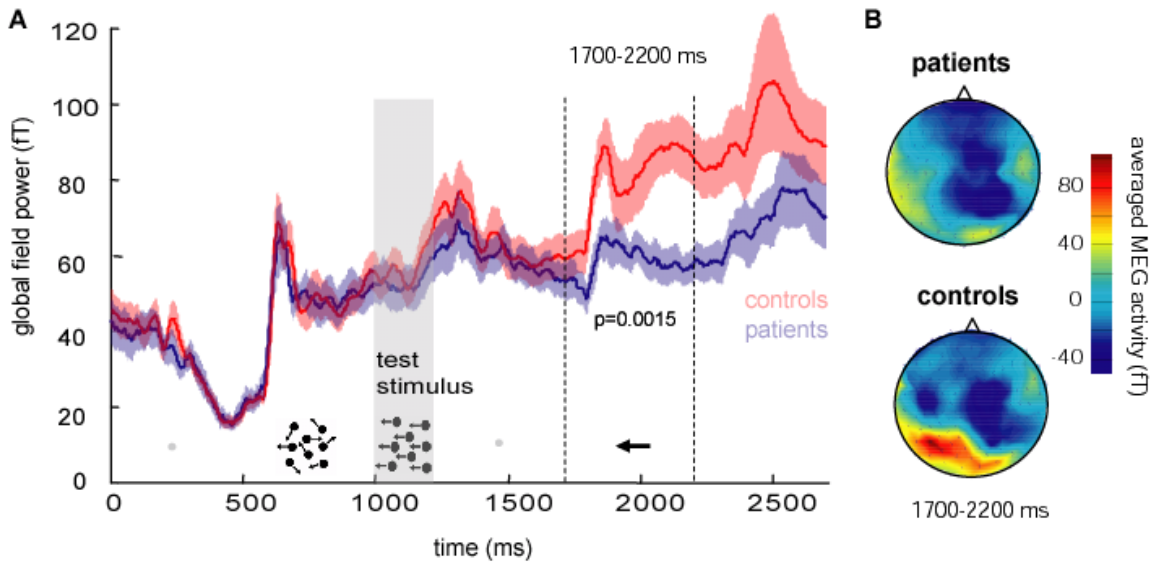

Figure 2) Time course of Global field power (GFP) and spatial activity distribution. A) Global field power (RMS of all sensors and subjects) depicted for patients (blue line) and controls (red line) over time. Within each stimulus period (indicated by insets on the bottom; test stimulus is additionally indicated by a grey bar) the responses were averaged and compared between groups, however, only during arrow presentation (1700 ms to 2200 ms marked by black broken lines) a significant difference between groups was present (T-test, p=0.0015). B) Spatial activity distribution over the brain (baseline corrected raw signal) averaged over the time period 1700- 2200 ms. The upper plot (right is right, nose up) is derived from the patient group, the lower one from the controls. The color within the plot codes the strength of activity in fempto Tesla.

As reported in a previous study healthy subjects show a linear increase in brain activity with increasing motion coherence (Händel et al., 2007). To see possible group differences in how motion coherence is represented in the cortex the dependency of brain activity on increasing motion coherence was calculated for cerebellar patients and healthy controls separately. As described in the methods, for each time sample a linear regression between GFP and coherence levels was calculated for each of the two groups resulting in the time course of beta values expressing the strength of the influence of motion coherence on cortical activity (and the corresponding p-values, Fig. 3). As expected, beta values grouped around zero for the time period before test stimulus onset since no coherence modulation was present yet. The important time period with respect to a strong dependency on motion coherence started around the offset of the test stimulus and lasted approximately until 100 ms before arrow presentation onset. Obtained beta values showed that the correlation with motion coherence, so clearly and convincingly shown for the control group, i.e. with high beta values and low p-values over quite a long period (about 100 ms), could only be anticipated within this time period for the patient group. MEG responses around the first time point for which a p-value below 0.05 was observed nicely showed the linear increase in response with increasing motion coherence for healthy controls and an only weak dependency on motion coherence in the cerebellar patients group. Additionally, there was no difference between groups for trials collected during 0% to 60% coherence whereas 80% and 100% coherency levels elicited a significantly ($p<0.05$, corrected) lower activity level in patients (Fig. 4).

Since one possible explanation of lower beta values in the group statistic of patients might be a greater variability in the latency of modulation a running linear regression for each subject separately was calculated with a time resolution of 10 ms. The maximal beta value between 150 and 600 ms after test stimulus onset was extracted for each subject and plotted against the individual perceptual threshold (Fig. 5A).

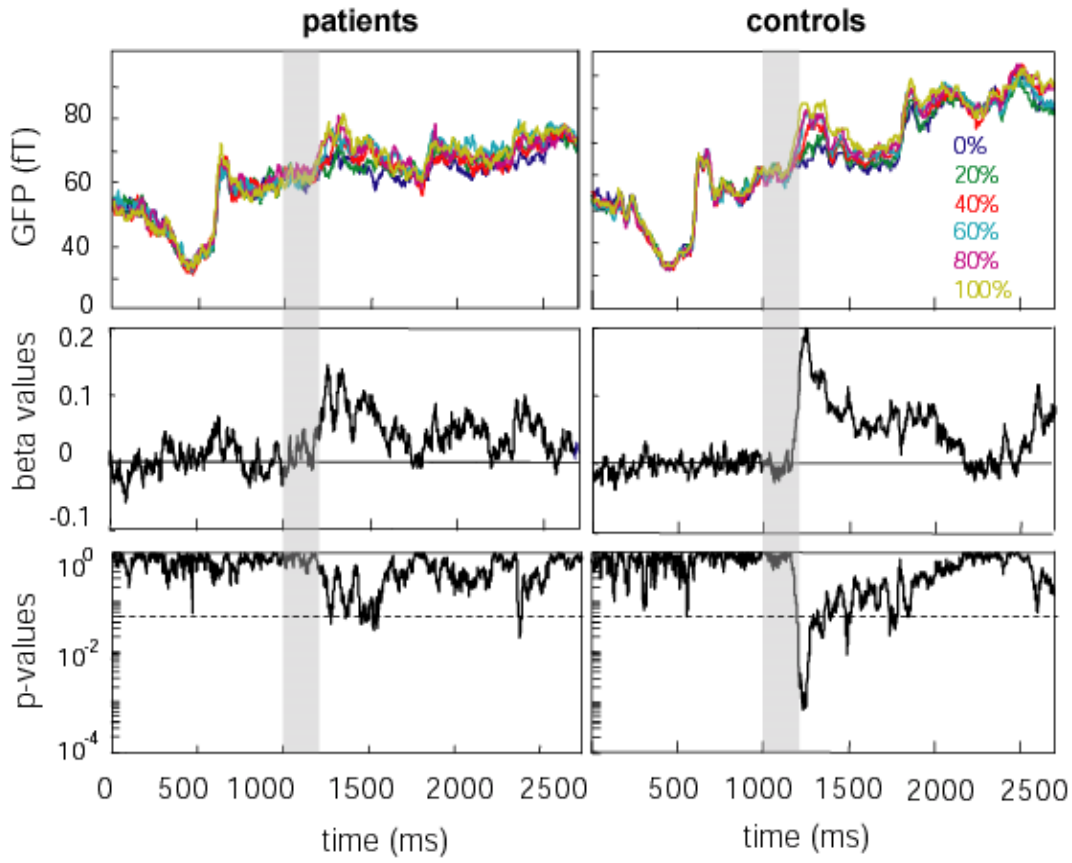

Figure 3) Dependency of the global field power (GFP) on visual motion coherence. Diagrams on the left depict results from the patient group, diagrams on the right from controls. GFP averaged over the subjects is plotted for the six coherence levels (indicated by different colors: blue=0%, green= 20%, red= 40%, cyan= 60%, magenta= 80%, yellow= 100%) as function of time. The lower panels show the beta and p values, respectively, obtained from a linear regression between GFP and motion coherence for each sample point. The broken horizontal line in the lowest two plots marks 0.05. Time of the test stimulus is indicated by a grey bar.

Beta values decreased significantly (linear regression: p=0.047, beta= -0.24) with increasing perceptual threshold which means the better the percept the higher the modulation of the magnetic response due to changing motion coherence. An even stronger correlation was observed between the latencies of the maximal beta values and the perceptual threshold. Fig. 5B shows that with decreasing perceptual ability also the latency of the maximal modulation is shifted to a later time point (linear regression: p=0.005, beta 3.13).

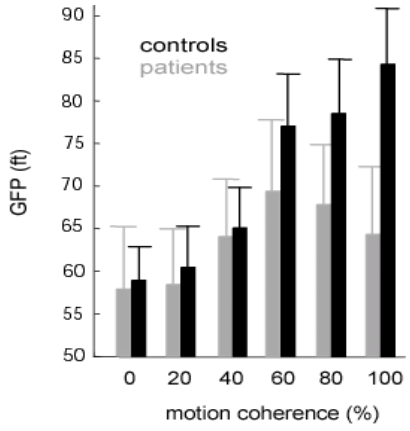

Figure 4) Response modulation with increasing motion coherence levels for patients (grey bars) and controls (black bars). GFP within 10 ms (6 samples) around the first time point p-values fell below 0.05 (controls: 230 ms, patients: 280 ms after test stimulus onset, see Fig. 3) were compared between groups for each coherence level separately by means of a T-test. Responses obtained for 80% and 100% coherence stimulation were significantly higher in the control group ($p<0.05$, corrected for multiple comparisons).

A quite qualitative difference between patients and controls could further be observed in the spatial distribution of the significant coherence modulation. Fig. 6 shows for both subject-groups the field distribution of the beta values over the brain with a time resolution of 50 ms starting from 100 ms to 350 ms after test stimulus onset. Whereas for both groups the beta values increased and became significant in occipito-temporal sensors lying contralateral to the stimulated visual hemifield 150 ms after motion onset, the following development was strikingly different. While the modulation for the healthy controls between 200 -250 ms could be seen for a bilateral occipito-temporal sensor distribution, i.e. contra- and ipsilateral to the stimulated visual hemifield, this behavior could at no time be observed for the patient group. So while the sensor distribution was quite similar for the contralateral temporo-occipital sensors there was no equivalent on the ipsilateral side for the cerebellar patient group.

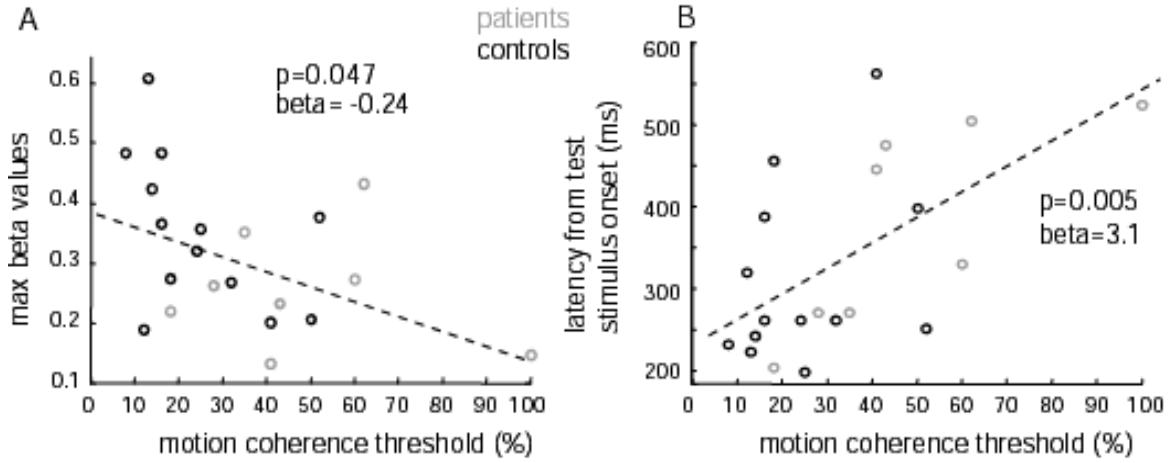

Figure 5) Correlation between the individual perceptual thresholds and maximal beta-values (derived from a linear regression over GFP and coherence levels for each subject separately) within the time period from 150 to 600 ms after test stimulus onset (or corresponding latencies, respectively). A) Maximal beta values (y-axis) plotted against the individual perceptual threshold (x-axis) of controls (black circles) and patients (grey circles). Beta values significantly decreased with increasing perceptual threshold as indicated by a significant linear regression (dashed line, beta= -0.24, p=0.047). B) Correlation between the latencies of the maximal beta values and the perceptual threshold (black =controls, grey =patients). With decreasing perceptual ability (x-axis) also the latency of the maximal modulation (y-axis) is shifted to a later time point (beta= 3.1, p=0.005).

Discussion

Damaged cerebellar-cortical projections are believed to cause changes in cortical activity which might result in a perceptual impairment. The present work tried to support this hypothesis using a model which seems ideally suited to link cortical responses to a perceptual deficit since both the impaired motion perception after cerebellar lesions as well as the cortical activity underlying motion processing are well studied.

Human whole brain activity was measured using magnetoencephalography while subjects had to discriminate the global motion direction (left or right) of a random dot kinematogram whose strength was systematically varied by the percentage of coherently moving dots. The expected perceptual impairment in the detection of the prevalent global motion direction as has been described previously (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier

et al. 1999; Jockisch et al., 2005) was clearly present in the group of patients with cerebellar lesions.

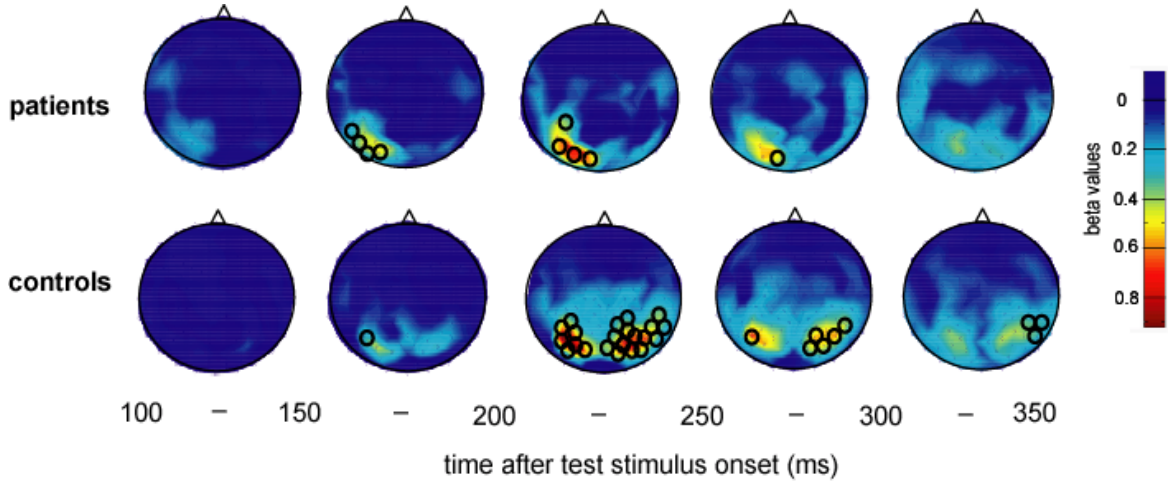

Figure 6) Spatial distribution of beta values derived from group analysis (linear regression over RMS values and coherence levels) over each sensor separately for patients (upper plots) and controls (lower plots) with a time resolution of 50 ms starting from 100 ms to 350 ms after test stimulus onset. Plots (right is right, nose up) are color coded, with bluish colors signifying low beta values and reddish ones high beta values. Significant sensors ($p<0.05$) are marked with a black circle.

It could further be shown that the perceptual ability was linked to the modulation of cortical activity elicited by the coherence modulated motion stimulus. In a previous study, using an almost identical stimulus, neuromagnetic responses linearly increased with rising motion coherence and the first development of this increase could be attributed to human area MT+ (Händel et al., 2007). Healthy controls in the present study showed a strong coherence dependent modulation at a similar latency, namely around 200 ms (even though stimulus presentation was reduced to 200 ms compared to 500 ms in the previous experiment). Also sensor localization was very comparable between studies strongly indicating area MT+ as part of the response source. When looking at the patient group modulation due to motion coherence could also be observed, however, in a clearly reduced way. This could indicate decreased activity modulation in area MT+ due to changed cerebellar input. Importantly, anatomical studies in the macaque have shown that there indeed exist connections between the cerebellum and the superior temporal sulcus at which caudal part area MT is located (for review see: Middleton and Strick, 2000; Dum and Strick, 2003). However, it can not be claimed that the decreased coherence modulation in cerebellar patients is exclusively caused by altered MT responses. First of all it was impossible to precisely localize the activity during the time period affected and secondly also other higher cortical areas (e.g. medial superior temporal area (MST): Celebrini and Newsome, 1994; lateral intraparietal area (LIP): Shadlen and Newsome, 1996, 2001) show coherence dependent activity and therefore can contribute to the modulation difference between groups.

Interestingly, the difference between patients and healthy controls was not a qualitative one as could be further shown with a correlation between the modulation strength (of brain activity) and the perceptual measurements. The stronger the coherence dependent modulation was the

better thresholds were achieved. This effect was significant if data from both groups were tested together and indicates that the prevalent coherence modulation is indeed linked to the perceptual ability. Since the change is not binary but gradual between patients and controls the cerebellum only seems to support motion processing in a way which might help the relevant cortical area to establish a good signal to noise ratio thereby increasing the possibility to perceive. The occurrence of the coherence dependent modulation per se, however, seems not only influenced by cerebellar input.

Also the latency of the maximal coherence modulation was correlated with the percept i.e. the later the peak of modulation was reached the more coherence was needed in order to detect the global motion direction. Again, this relationship was visible if healthy subjects as well as cerebellar patients were included in the regression. It has been argued that directional signals originating from area MT have to be integrated over time in order to reach a decision about a global motion direction (Shadlen and Newsome, 2001). A critical perceptually relevant threshold might be reached early if the modulation i.e. the differentiation between signal and noise is strong and on the other hand processing would need more time if only a weak modulation is present. The patient who did not perceive any motion direction showed a coherence dependent modulation even though it was very small and was basically rising during the whole time (indicated by the latency of the maximal beta value). In line with the above mentioned idea one could interpret this finding in such a way that even though modulation was present there was not enough time to reach an input based decision by adding the information from the weak activity modulation. This would further mean that the presentation time is more important for subjects with a low coherence modulation, an interpretation further supported by the findings that also cerebellar patients with a pronounced deficit can reach normal thresholds if the presentation duration of the stimulus is increased sufficiently (Thier et al., 1999). This timing component might also explain why motion perception deficits in cerebellar patients have only been reported for the central visual field so far. It has been shown by Carrasco and colleagues (2003) that stimuli of identical size are processed up to ~90 ms faster if presented at an eccentricity of 9° compared to 4° which can be partly explained by the difference in the physiology of the different ganglion cells. This would mean that for central stimulation presentation time is more critical and a deficit might be observed centrally but not peripherally despite identical stimulus duration A first hint that this is indeed the case was given by Scheerer and colleagues who reported that cerebellar patients show impaired motion coherence thresholds for a coherence modulated stimulus presented for 500 ms centrally but that no deficit could be found if the same stimulus was presented eccentrically for the same duration (Scheerer et al., 2004). However if the presentation in time is reduced substantially for peripheral presentation (200 ms, as in our study) again a deficit can be observed.

A quite qualitative difference between patients and controls was found in the spatial distribution of coherence dependent activity modulation over the brain. While healthy controls exhibited, after a first modulatory peak in temporococcipital sensors contralateral to the stimulated visual hemifield, a bilateral coherence modulation starting after motion offset, cerebellar patients did not exhibit such a change to the ipsilateral side at any time. Area MT+ can be activated bilaterally by one sided stimuli in humans (Tootell et al., 1995) even without callosal connections (Clarke et al., 2000) so bilateral activation is most likely due to receptive

fields overlapping into the ipsilateral hemifield. While only a relatively small number of neurons in monkey area MT show an ipsilateral representation (Desimone and Ungerleider, 1986; Maunsell and Van Essen, 1987) areas following MT, like e.g. area MST, show receptive fields which mostly cover parts of both hemifields (Desimone and Ungerleider, 1986; Saito et al., 1986). Unfortunately, with the method used it was impossible to pin down the responsible area for the difference in ipsilateral activation between patients and controls. The use of imaging techniques offering higher spatial resolution should help to solve this question.

A further difference between cerebellar patients and controls was a significantly reduced overall activity in patients during the last part of the stimulus i.e. when the direction of the test stimulus had to be compared to the presented arrow direction. During this time period motion processing was likely to be finished but processes related to working memory specifically to the retrieval of information stored in memory might be influential. It has been claimed that working memory is related to a cortico-cerebellar interaction since cerebellar patients show a working memory deficit (e.g. Ravizza et al., 2006) and functional neuroimaging identified cerebellar regions to be activated in verbal working-memory tasks (Chen and Desmond, 2005). However, a resent experiment by Ziemus and colleagues (2007) studying working memory with fMRI in cerebellar patients showed a pronounced increase in BOLD activity in the patient group which is contrary to the decreased activation found by us. Changed motor-related processes seem therefore more likely to cause the differential activity between cerebellar patients and controls: During the time period exhibiting this differential activity, the decision about the motor response and its preparation had to be made i.e. what finger must be lifted in order to give the correct answer. The activity level during this time period did not correlate with the perceptual deficit, therefore, the difference in activation between groups might depict a general change in premotor processing due to altered cerebellar output. Unfortunately, no information about the origin of this differential activation could be obtained.

Due to the increased range in perceptual thresholds by cerebellar patients a mechanism could be demonstrated which links cortical coherence modulation and its corresponding latencies to the ability to detect motion direction in a coherence modulated display. Besides this rather general relationship between percept and a coherence dependent modulation during motion processing, also a qualitative difference in cortical activity between cerebellar patients and controls could be shown, namely an absence of ipsilateral activity modulation as observed in normal controls. Even though the precise character of the cerebellar influence is unclear this study is to our knowledge the first to show that the cerebellum indeed changes cortical activity aligned to a changed percept.

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2.4 Neuromagnetic activity, including RMS values, delta and alpha oscillations, differentiates between correctly and incorrectly perceived visual motion.

Introduction

One intriguing observation about our perceptual performance is that on times we perceive a certain stimulus correctly whereas on others we are not able to even though we deal with the exact same stimulation. There have been approaches to study brain activity during such situations of perceptual errors in order to identify mechanisms which might influence the percept.

V1 neurons in the macaque e.g. are described to fire significantly weaker during trials which lead to incorrect answers compared to correct ones (Li et al., 2006; Roelfsema and Spekrejse, 2001; Super et al., 2001). The same effect has been found in the rhesus monkey for neurons in the prefrontal area (Kim and Shadlen, 1999), the lateral intraparietal area (LIP; Shadlen and Newsome, 1996; 2001) as well as for neurons in the monkey middle temporal (MT) area (Bisley et al., 2004, Oliveira et al., 1996; Seidemann and Newsome, 1999, Cook and Maunsell, 2002). Concerning human fMRI inconsistent findings have been reported with some studies revealing a general increase in activation linked to correct answers for early visual cortical areas such as V1, V2 and V3 (Ress and Heeger, 2003) whereas others don't (Tjan et al., 2006). For human area MT+ (a complex of various extrastriate areas including area MT) Shulman and colleagues (2001) found a general increase in BOLD activation linked to correct answers compared to misses in a motion detection task.

Further ideas suggest that not only the strength but also the distinct timing of activity might decide on the perceptual outcome as indicated by the involvement of oscillatory brain activity in perceptual processes (Basar et al., 2000). First evidence has been reported by Kompass and colleagues who showed that slow delta amplitudes (< 3.5 Hz) decreased if motion was perceived in an ambiguous apparent motion task (Kompass et al., 2000). Similarly, attention has been shown to alter the amplitude of such oscillations (3+/-2 Hz) in a motion detection paradigm along with the ability to correctly perceive the motion direction (Händel et al., submitted a).

The aim of the present study was to test if a direct link between perception and oscillatory cortical responses could be found by comparing magnetic activity elicited by correctly and incorrectly perceived trials after identical stimulation. To this end visual motion rendering answers close to the individual chance level was presented during magnetoencephalography (MEG) recordings in order to obtain a sufficient number of correct and incorrect trials. As will be shown, a general increase in magnetic response was observed and additionally a decrease in amplitude for correctly compared to incorrectly answered trials in the delta (3 +/-2 Hz) and alpha-band (10 +/-3 Hz). An account of the data using different analysis methods has been given elsewhere (Händel et al., submitted b).

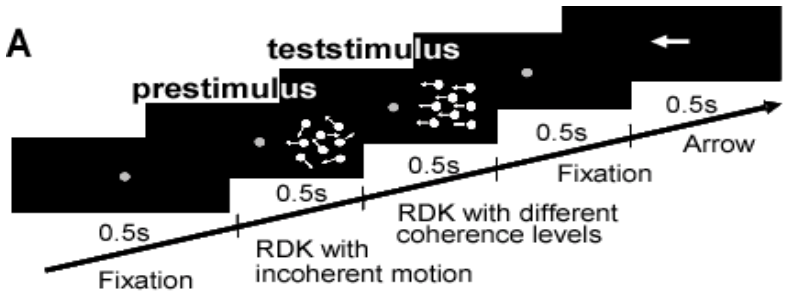
Methods

Seven healthy subjects, 3 males and 4 females with a mean age of 29 (+/- 2.9) years participated in this study. All subjects had normal or corrected to normal vision. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the

guidelines of the local ethics committee of the medical faculty of the University of Tübingen, which approved the study.

Procedure and stimulus material: Subjects were seated upright in a magnetically shielded room (Vakuum- Schmelze, Hanau, Germany) and were instructed to sit as motionless as possible during the MEG recording. Stable posture was supported by a chinrest attached to the MEG chair. The computer generated visual stimuli were rear projected onto a large translucent screen (DLP-projector (digital light processing), frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 92 cm in the magnetically shielded room. Viewing was binocular.

The visual stimulus consisted of 5 periods, each lasting 500ms (see Fig.1) each being observed by the subjects during controlled stationary fixation. During the first 500 ms, only a stationary red dot (diameter 10 arcmin) was presented in the middle of the screen which served as the fixation target and which remained visible for a total of 2 s. The first 500 ms period was followed by a second one introducing a random dot kinematogram (RDK) which covered a square of 16 x 16 deg and was centered 15 deg right of the fixation point. The RDK consisted of 1500 white squares (side length = 8 arcmin, lifetime = 1000ms, dot density ~ 6dots/deg2, luminance 47cd/m2) all moving incoherently, i.e. in all possible directions with a resolution of 1 degree, at a common speed of 6deg/s. After the presentation of this first RDK that will also be refered to as the "prestimulus", a second RDK, the "test stimulus", started. The properties of this second RDK were identical to those described for the prestimulus except that a certain amount of dot elements moved coherently in the same direction (either to the left or to the right). Specifically, the percentage of coherently moving dots was dependent on the individual threshold of the subject identified as will be described below. After a subsequent second fixation period, an arrow was presented in the middle of the screen pointing either to the left or to the right side as randomly chosen by the stimulus generator. Subjects were instructed to keep fixation as accurately as possible during the whole trial and to indicate by lifting their right or left index finger whether the motion direction of the dots of the test stimulus was identical (right index finger) or opposite (left index finger) to the pointing direction of the arrow. Subjects were instructed to guess if they were not sure about the direction seen (forced choice). Finger movements were detected using a light barrier. Note that the motor response could not be planned until the arrow had been presented, guaranteeing that the MEG signals during the first 1000ms after test stimulus onset were not related to movement preparation. The individual measurement consisted of 420 single trials. The individual threshold was identified beforehand by using a set of trials modulated by a staircase procedure in which the coherence level was varied until 70% of all trials would be answered correctly. This coherence level was than used for further stimulation. The 7 subjects measured showed a mean percentage of correctly answered trial of 63 +/-5 and were stimulated with 13 +/-6% motion coherence. During all experiments, eye movements were monitored using a homemade video system taking the pupil's centre as measure of eye position. Recordings were stored at a sampling rate of 50 Hz and analyzed offline in order to assess the quality of fixation. In particular, oculomotor parameters (i.e. eye velocity, eye position and number and amplitude of saccades) showed no dependencies on the ability to correctly perceive the motion direction (paired T-test >0.05).



B

subjects	1	2	3	4	5	6	7
% correct responses	63	59	65	68	60	57	71
% motion coherence	7	6	24	11	14	14	14

Figure 1) Experimental paradigm and stimulus specifications for the different subjects. A: The stimulus consisted of 5 periods each lasting 500 ms. In contrast to the "prestimulus", a random dot kinematogram (RDK) consisting of incoherent motion, the following "test stimulus" involved the presentation of coherent motion the percentage of which was adjusted in each subject in order to obtain ~70% correct responses. Coherent motion was directed either to the left or to the right. Subjects had to indicate whether the motion direction of the coherently moving dots of the test stimulus was identical or opposite to the pointing direction of the arrow presented at the end of the trial. B: Percentage of correct responses and amount of motion coherence (percentage of coherently moving dots) used for stimulation are listed for each of the seven subjects separately. Motion coherence remained the same through all trials during MEG recording.

Recording and analysis of the MEG signals: Neuromagnetic activity was recorded using a whole-head MEG system (CTF Inc., Vancouver, Canada) comprising 151 first-order magnetic gradiometers. The signals were sampled at a rate of 625 Hz. Recording epochs lasted from stimulus onset to arrow offset plus 200 ms, leaving 2700 ms of recording time for each trial. The subject's head position was determined at the beginning and at the end of each recording session by means of localization coils fixed to the nasion and preauricular positions to ensure that head movements did not exceed channel separation. MEG recordings were baseline corrected (subtracted by baseline = 240 to 499 ms after stimulus onset) and trials contaminated by muscle activation or other artifacts defined by activity surpassing 3 times the normal MEG amplitude were excluded.

Analysis of the evoked MEG responses: In a first attempt to search for MEG activity reflecting correct and incorrect answers the root of the mean squared magnetic fields (RMS) was calculated for each subject, each sensor and each sample separately. RMS values averaged over sensors resulted in the time course of the global field power (GFP). For further analysis RMS values were averaged for correct and incorrect answers and a paired T-test (correct vs. incorrect) over 6 consecutive samples and 7 subjects was calculated for each sensor separately (MATLAB, version 6.5.1). The time window (6 samples ~10ms) was shifted from 500 ms to 2400 ms in steps of 1 sample (sliding time window, Rugg et al, 1995). Those sensors were selected as being significantly different which showed all p-values during a 300ms epoch (= 31 consecutive samples) below a value of 0.001. To demand neighboring events to be significant at the same time is a quite common approach (e.g. Fell et al., 2001; Trautner et al., 2006). Additionally, two neighboring sensors had to be significant.

Frequency analysis of the MEG recordings: In order to test whether correlations between MEG responses and percept might also be confined to specific frequency bands, a spectral analysis of the MEG signals was performed. This analysis was conducted on single trial basis in the range of 1–100 Hz (1.23 Hz bins) for five partially overlapping 700 ms time windows which were defined by the five different 500 ms epochs of stimulation (compare Fig.1) each being expanded by the 100 ms interval immediately preceding and following the individual epoch. The resulting recording points were downsampled and zero-padded to obtain 256 points. To reduce the frequency leakage the records were multiplied by Welch windows as recommended by Press et al. (1992). A fast Fourier transform was calculated for each time window, each channel and each trial separately and only then, spectral amplitudes (in the given time window) were averaged over trials for correct and incorrect answers. The influence of correct percept on the spectral amplitudes was assessed by a T-test performed on the group of 7 subjects and for each frequency band (width: 1.23 Hz) and channel separately. Significance was assumed if two adjacent frequency bins and two adjacent sensors showed p-values below 0.043 which was calculated as p-threshold = sqrt (sqrt (0.05/ (number of channels=151 x number of frequency bins=100))) (Fell at al., 2001). Only those frequency bands that showed significance were analyzed further.

To quantify the amplitude differences between correct and incorrect trials MEG recordings were baseline corrected and Gaussian filtered for the two frequency bands which did show a significant modulation by the answer type (i.e. 3 Hz +/-2 and 10 Hz +/-3, respectively). Data was amplitude demodulated by means of a Hilbert transformation, trials were averaged over the 2 different answer possibilities (correct or incorrect) and further analysis was conducted for the time period between 500 and 2400 ms. As described for the RMS values, a T-Test between correct and incorrect trials was calculated over the 7 subjects for each sensor but only for one sample at a time in order to avoid any possible effect due to the previous filtering. Those sensors were selected as being significantly different which showed all p-values during a 300 ms epoch (= 187 samples) below the value of 0.05. The epoch was moved across the whole time course of the stimulus in steps of one sample as described above. Again, two neighboring sensors had to be significant.

Source localization: Alpha activation was localized by means of a beamformer algorithm. Three-dimensional imaging of brain activity was performed using synthetic aperture magnetometry (SAM; Robinson and Vrba, 1999). SAM is a type of minimum variance beamformer which is sensitive for 4 dimensions (voxel location and source orientation) and therefore might result in a better spatial resolution as compared to conventional beamformers (for details see, e.g. Vrba and Robinson, 2002). This specific type of minimum variance beamformer, implemented in the CTF software, was calculated for the 8-11 Hz frequency band in the fixation period after motion presentation (1.5 to 2.0 sec). For each subject a pseudo-T statistic was calculated to estimate the difference in source power between the correctly and incorrectly answered trials at the given target voxel (side length 1 cm; Robinson and Vrba, 1999).

Results

Three activity differences linked to the ability to correctly perceive motion direction were observed, one in the general magnetic response and two concerning the amplitude of oscillations in the delta and alpha frequency band respectively.

Concerning the evoked magnetic response an increase in activity for correct compared to incorrect trials was already observed if the average over all sensors (= global field power) was examined. While the response strength until prestimulus onset was identical for correctly and incorrectly answered trials activity during prestimulus presentation rose more strongly for correct trials as can be seen in Fig. 2. There are two groups of sensors that showed a significantly higher activity for correct compared to incorrect trials, one lying over the contralateral occipito-temporal cortex and the other one over frontal areas (Fig. 2C).

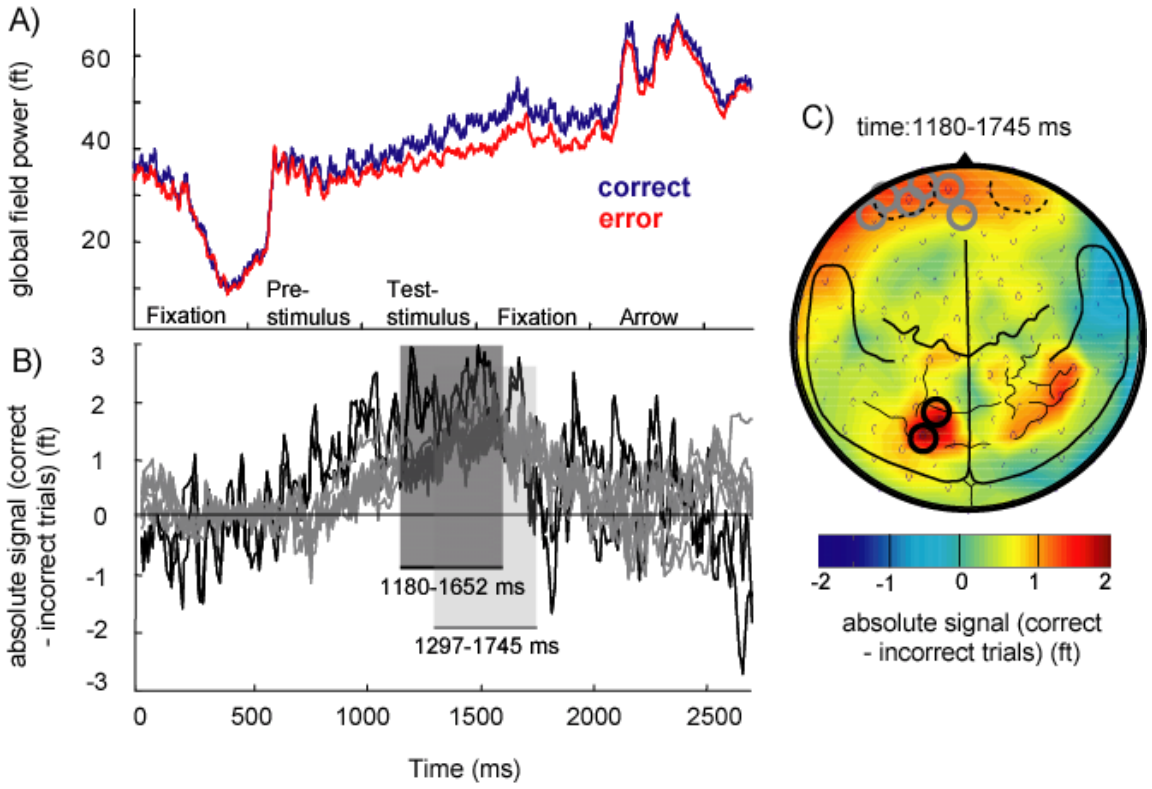


Figure 2) Dependency of the global field power on correctly and incorrectly detected motion direction. A: Averaged magnetic response over the 7 subjects are plotted for correctly (blue) and incorrectly (red) answered trials as function of time. B: The difference between correctly and incorrectly answered trials for sensors indicated in C. The color of the line plots is in accordance with the color of the sensors shown in C i.e. black lines correspond to the two contralateral occipito-temporal sensors, grey lines to the frontal ones. Transparent bars in the same color mark the averaged time period in which the sensors exhibit a significant difference between correct and incorrect trials. C: Amplitude differences between correctly and incorrectly answered trials (color coded) averaged over the time period sensors were significant (1180:1752 ms) are projected onto a two-dimensional MEG sensor map (seen from above, nose up). Yellow to red colors signify that amplitudes are higher for correctly answered trials, dark to light blue colors signify the contrary. Circles mark significant sensors.

Occipito-temporal sensors significantly differentiated between correct and incorrect trials during the presentation of the coherent motion stimulus at a latency of 1180 ms and the significant effect lasted for 472 ms (+/-67 ms STD, Fig. 2B). The second group, i.e. 5 sensors

over the frontal cortex, also showed a higher activity during correct trials but reached significance 117 ms later (mean latency 1297 +/-107 ms STD) and persisted on average 448 ms (+/-92 ms STD) reaching into the fixation period following the coherent motion presentation (Fig. 2B). During all other stimulus epochs no significant difference was observed.

Secondly, a decrease in amplitude of oscillation in the 3 Hz (+/- 2 Hz) frequency band was found for correctly compared to incorrectly answered trials. At an averaged latency of 1083 ms (+/-33 ms STD) after stimulus onset, namely during test stimulus presentation, this difference reached significance in two occipito-temporal sensors and lasted 355 ms (+/-5 ms STD, Fig. 3A).

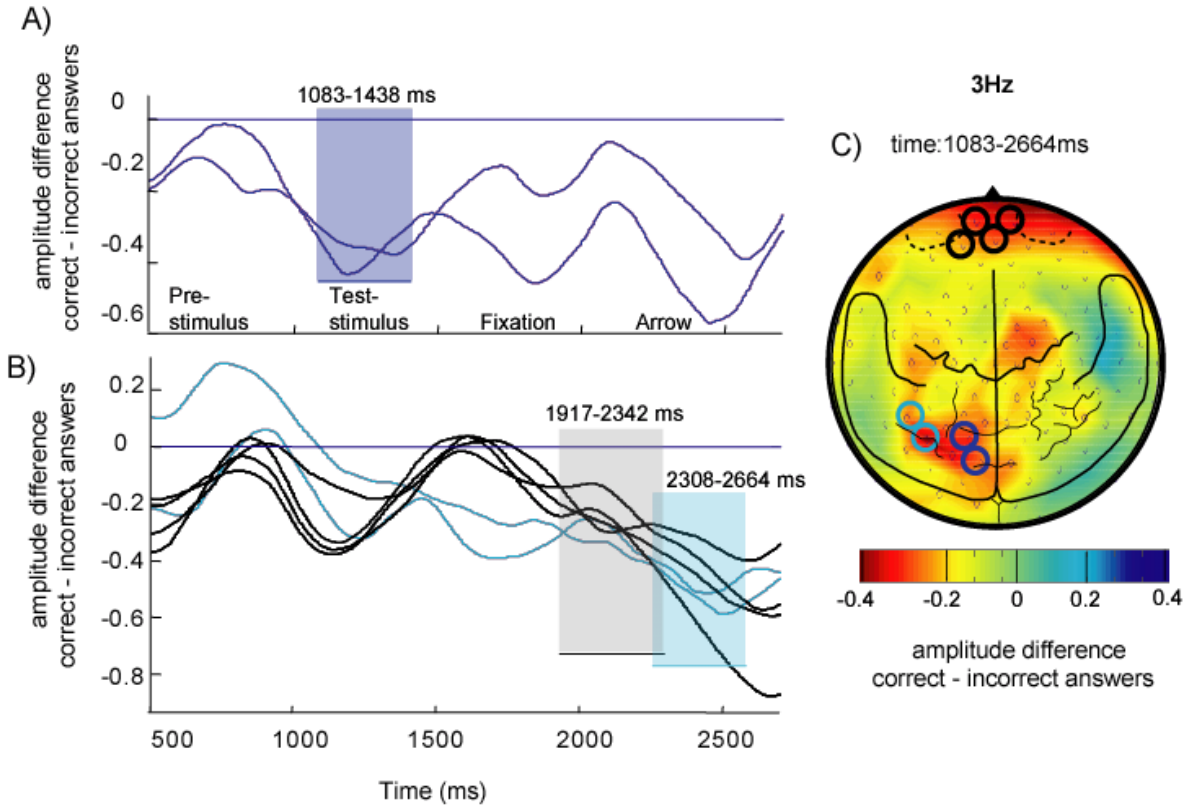


Figure 3) Dependency of 3 (+/-2 Hz) oscillations on correctly and incorrectly detected motion direction. Negative values indicate that the amplitude for correctly answered trials are lower than for incorrectly answered ones. The color of the line plots in A and B is in accordance with the color of the significant sensors marked with a colored circle in C. Transparent bars in the same color mark the averaged time period in which the sensors exhibit a significant difference between correct and incorrect trials. A: Amplitude values of the 3 Hz frequency band averaged over the 7 subjects are plotted as difference between correctly and incorrectly answered trials as a function of time for contralateral occipito-temporal sensors (light blue) indicated in C. The x-axis starts with the presentation of the first RDK (incoherent motion, onset at 500 ms). B: The difference between correctly minus incorrectly answered trials for contralateral occipito-temporal sensors (dark blue) and frontal sensors (black) indicated in C. C: Amplitude differences between correctly minus incorrectly answered trials (color coded) averaged over the time sensors were significant (1083:2664 ms) are projected onto a two-dimensional MEG sensor map (seen from above, nose up). Yellow to red colors signify that amplitudes are lower for correctly answered trials, dark to light blue colors signify the contrary. Circles mark significant sensors.

A second set of sensors reached significance at the time of the second fixation period (Fig. 3B). Specifically, four frontal sensors (latency 1917 +/-62 ms STD) showed significance for 425 ms (+/-37 ms STD) and two occipito-temporal sensors (latency 2308 +/-92 ms STD) were

significant for 356 ms (+/-59 ms STD). Frontal and occipito-temporal sensors showed an amplitude decrease for the correctly answered trials for all significant time periods.
As third effect alpha band activity (10 +/-3 Hz) showed a decrease in amplitude for correctly answered trials. Two groups of occipito-temporal sensors exhibited a significant effect, one lying contralateral to the visually stimulated hemifield and one ipsilateral (Fig. 4C).

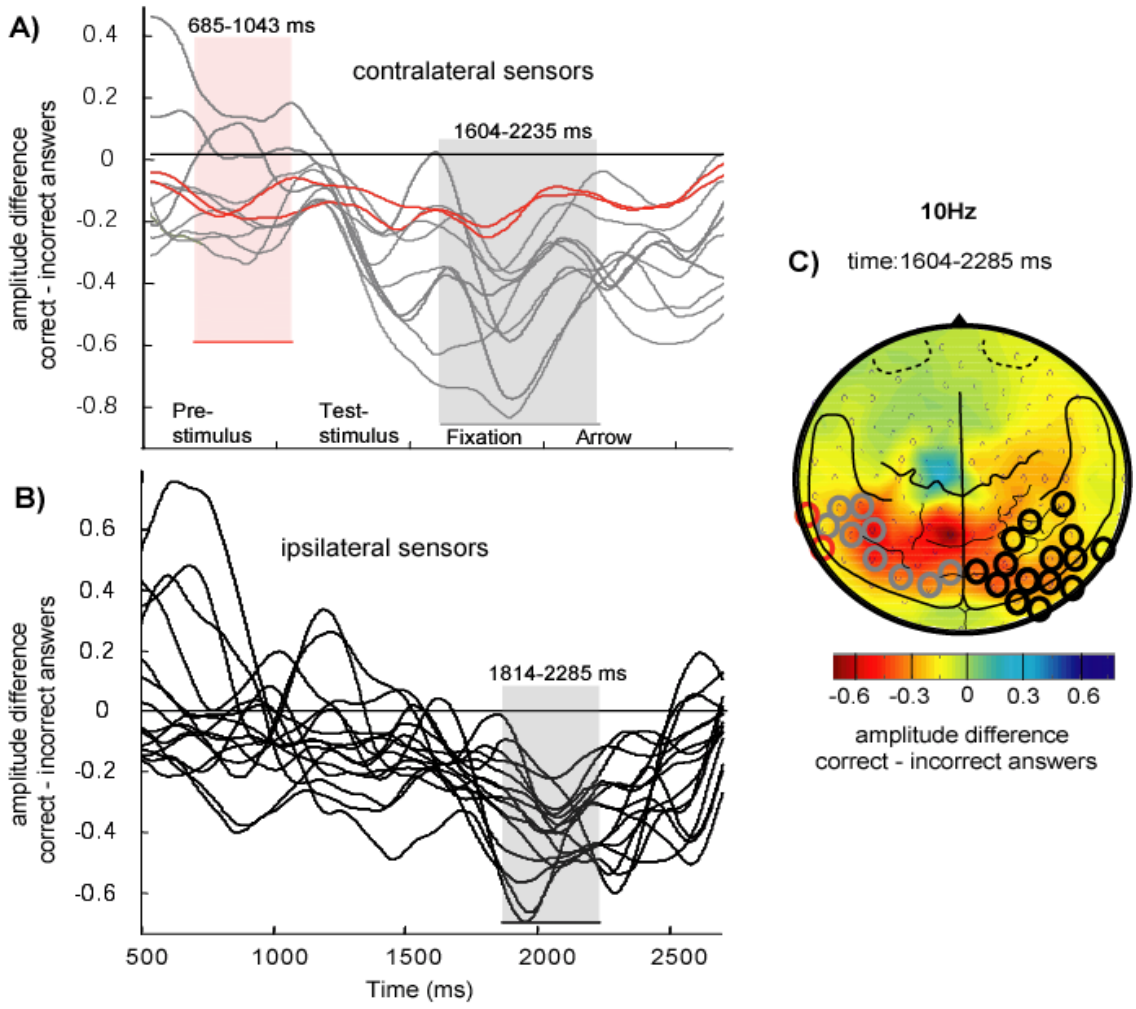


Figure 4) Dependency of 10 (+/-3 Hz) oscillations on correctly and incorrectly detected motion direction. Negative values indicate that the amplitude for correctly answered trials are lower than for incorrectly answered ones. The color of the line plots in A and B is in accordance with the color of the significant sensors marked with a colored circle shown in C. Transparent bars in the same color mark the averaged time period in which the sensors exhibit a significant difference between correct and incorrect trials. Amplitude values of the 10 Hz frequency band averaged over the 7 subjects are plotted as difference between correctly and incorrectly answered trials as a function of time. The x-axis starts with the presentation of the first RDK (incoherent motion, onset at 500 ms). A: The lineplots are extracted from the sensors marked with a black or red circle in C over the contralateral occipito-temporal area. Two ventrally lying sensors (red) show a weak but significant decrease for correct trials compared to incorrect ones during the prestimulus. All contralateral sensors showed a strong decrease in amplitude after coherent motion offset as indicated by the transparent bars. B: Ipsilateral sensors (grey circles) show a significant amplitude decrease for correct trials after coherent motion offset. C: Amplitude differences between correctly and incorrectly answered trials (color coded) averaged over the time period 1604:2285 ms are projected onto a two-dimensional MEG sensor map (seen from above, nose up). Yellow to red colors signify that amplitudes are lower for correctly answered trials, dark to light blue colors signify the contrary. Circles mark significant sensors.

Within the contralateral group the two most ventrally lying sensors (Fig. 4A) showed a small but significant decrease for correct trials compared to incorrect ones during the prestimulus period (685 +/-7 ms, lasting 358 +/-61 ms). During the second fixation period 11 contralateral sensors showed a strong decrease in amplitude (latency of 1604+/- 166 ms STD) which lasted about 631 ms (+/-368 ms STD). Also significant ipsilateral sensors (Fig. 4) showed a decrease for correct trials during the fixation period after test stimulus offset at a latency of 1814 (+/-126 ms STD) persisting during most of the arrow presentation (471 +/-120 ms STD). The difference between correct and incorrect trials during the fixation period started on average more than 200 ms earlier in sensors lying contralateral to the visually stimulated hemifield.
In order to asses the source of alpha amplitude differences the source power was calculated for the 8-11 Hz frequency band during the second fixation period using SAM and compared between correct and incorrect trials by means of pseudo-T statistics (for details see methods). Voxels showing the maximum T-values (mean T = 2.3 +/-0.6) were located in occipital cortex mostly contralateral to the stimulated side indicating an activation of early visual cortex such as areas V1 and V2 (Fig. 5). For 2 out of 7 subjects SAM revealed no voxels with a significantly higher activation for correctly compared to incorrectly answered trials. One subject had an additional peak in the PO region whereas another one showed an additional frontal peak.

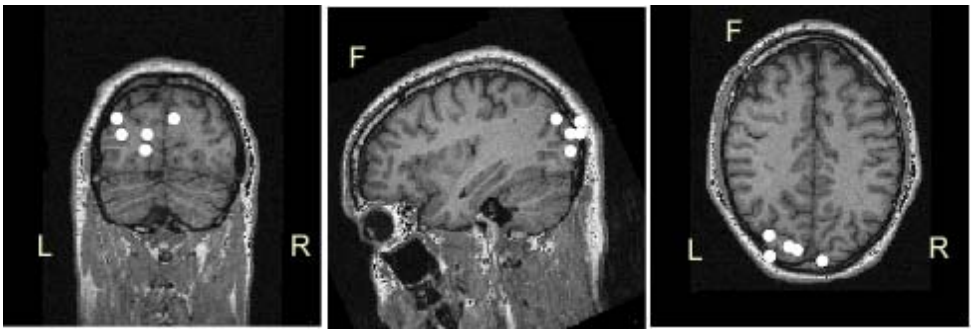


Figure 5) Localization of voxels with maximum T-values obtained from pseudo-T statistics estimating the difference in source power between correct and incorrect trials (results from 5 out of 7 subjects). Source power was obtained using a minimum variance beamformer (SAM) for the 8-11 Hz frequency band for 1500-1750 ms. R: right; L: left; F: frontal.

Analyses of eye-movements did not reveal any significant difference between correctly and incorrectly answered trials within the different oculomotor parameters such as slow eye drifts (eye velocity), deviations from the fixation point (eye position) or the number and amplitude of saccades ($p>0.05$ uncorrected). Incorrect responses should therefore not reflect oculomotor deficiencies.

Discussion

Three activation pattern, namely the RMS values, the delta band and the alpha band amplitudes, which have been previously found to be linked to altered motion coherence (Händel et al., 2007) seem also influential of or influenced by the ability to correctly perceive coherent motion stimuli near the perceptual threshold.

A general increase in the magnetic field response was found for correctly compared to incorrectly answered trials over contralateral occipito-temporal and frontal sensors. Occipito-temporal sensors started to show this significant increase 180 ms after coherent motion onset. Location and timing agree with previous findings: Rodriguez and coworkers (2006) showed that evoked potentials, ascribed to the extrastriate cortex, increased in amplitude for correctly identified motion directions compared to incorrect trials at about 200 ms after stimulus onset. Human fMRI confirmed an increase in activation of area MT+ for correctly perceived motion directions (Shulman et al., 2001). These fMRI and EEG-ERP results were interpreted as depicting the accumulated sensory information available for the decision. The more information can be accumulated the more likely a correct response will follow. That magnetic responses generated in area MT+ are influenced by the amount input signal is inline with previous results showing that increasing motion coherence, providing enhanced sensory information, also leads to a higher magnetic field response in the extrastriate cortex (Aspell et al., 2005; Händel et al., 2007).

However, the activity pattern described in the study at hand seems likely to be distinct from the one modulated by sensory information. This is indicated by the appearance of a second frontal source as well as the difference in the temporal structure of the effects. Looking at the plotted difference in Fig. 2 it is striking that, even though significance was reached at a latency of 180 ms, the effect seems to have started already before the onset of the coherent motion. In contrast, coherence dependent modulation was completely absent until about 200 ms after motion onset (see Händel et al., 2007). Rather than an accumulation of relevant information the present activity might therefore reflect a fronto-occipital network related to an increase of alertness or temporal expectancy to the onset of the to-be-interpreted stimulus. Only recently it has been shown that information about time intervals can be used dynamically to direct visual attention (Coull and Nobre, 1998). This temporal attention can improve the behavioral performance as to shorten reaction times in detection (Coull and Nobre, 1998, see Nobre, 2001 for review) as well as discrimination tasks (e.g., Correa et al., 2004, Doherty et al., 2005, for review see Correa et al., 2006). Interestingly, a resent publication by Correa and colleagues (2006) reported an increase in EEG response to a cue which indicated that the target will appear early compared to a response following the cue for late target presentation. This increment took place before the target was visible over the occipito-parietal area. A similar mechanism might be involved in our task since the timing structure is very predictable thereby offering the possibility to anticipate the target (coherent motion) onset. Secondly, as pointed out by Correa and colleagues (2006), temporal attention is most likely strained if perceptually demanding tasks have to be solved. Our task was extremely challenging since the presented motion coherence was selected individually beforehand as to make sure that only a relatively low percentage of trials could be answered correctly. It seems therefore possible that trials were more error-prone in which the timing structure was ignored and preparation and, consequently, the increased response before the target presentation was not induced.

A second component exhibiting a significant difference for correctly compared to incorrectly answered trials was found in the 3+/-2 Hz frequency band showing lower amplitudes for correct trials during test stimulus presentation. Interestingly, amplitudes in this frequency band seem to be influenced by the attentional state of the observer during target presentation

as reported recently. Specifically, if attention was focused on a stimulus containing high motion coherence amplitudes were increased, however, stimulating with low motion coherence led to a decrease in amplitude if attention was directed towards the stimulus (Händel et al., submitted a). Also In the present study effectively focused attention might have caused correct percept and consequently also the amplitude change could reflect an effect of attention on brain activity. If attentional effects are considered to be the main cause for perceptual differences and since the individual stimulation of the present study was of low motion coherence a decrease in amplitude for correct trials was expected. The observed decrease for correct answers could further be interpreted in line with the idea that attention might enhance preferred information while any deviating interfering information might be suppressed. In our specific paradigm, a high percentage of incoherent motion is equivalent to a high fraction of noise. In correct trials the effective inhibition of this noise might lead to an amplitude decrease.

Later during the trial, i.e. during the period were an arrow was presented which delivered the information necessary to decide about the correct motor response, a frontal and parietal decrease in the 3 Hz amplitude for correctly compared to incorrectly answered trials was found. In another low frequency band, i.e. theta (4-8 Hz), activity has been associated with memory processes (Klimesch et al., 2001, Sederberg et al., 2003, Osipova et al., 2006; for review see Sejnowski and Paulsen, 2006; Kahana, 2006). However, if our amplitude modulation was related to memory one would expect an altered signal already during the main memory period i.e. during fixation following the motion stimulus and preceding the presentation of the arrow. A special feature of the time period in which our modulation was most prominent is that a decision had to be formed as to how to interpret the information of the arrow, i.e. is the direction of the presented arrow the same (answer with the right hand) or different (answer with the left hand) to the previously presented motion direction. The modulation during this time period might therefore resemble a comparison of present information (arrow) with a stored one (direction). This idea has previously been discussed for the somatosensory system and single cell recordings in monkeys performing a quite similar task concerning the course of the paradigm also indicate an involvement of the prefrontal cortex in comparisons between stored and new information (Brody et al., 2002).

The third component for which a significant effect between correctly and incorrectly answered trials was observed was prevalent in the alpha band. In this frequency band contra- and ipsilateral occipital sensors, ascribed to early visual cortex, showed as main effect a decrease in amplitude for correctly answered trials during the fixation period after coherent motion presentation. Contralateral occipital sensors showed this decrease on average 200 ms earlier than the significant occipital sensors lying ipsilateral to the visually stimulated hemifield. This suggests a subsequent transfer from the contra- to ipsilateral hemisphere. In contrast to the earlier notion that alpha synchronization indexes ‘cortical idling’, i.e. a default resting state, it is becoming apparent that alpha oscillations indicate an active mechanism suppressing cortical activity that might interfere with task relevant signal processing (e.g. Ward, 2003). In line with this interpretation are recent studies which showed that dependent on the modality at which attention had to be directed alpha amplitude increased over the deliberately to-be-ignored modality processing area (Foxe et al., 1998, Fu et al., 2001, Jokisch and Jensen, 2007). Also within one modality Worden et al. (2000) demonstrated that spatial

shifts of visual attention were paralleled by sustained focal increases of alpha activity in a retinotopically specific manner. They showed that if attention was directed towards a location alpha would increase in those visual cortical areas not coding for this specific location. Also the finding that alpha activity in early visual cortex increases with decreasing motion coherence after motion offset supports this interpretation (Händel 2007). Alpha, if seen as a mechanism that gates incoming information, should be strongest if the preceding stimulus is complicated and needs more time to be processed (low motion coherence) and therefore has to be protected from new and perturbing input. In line with this hypothesis the increased alpha amplitude for incorrect trials was interpreted as an expression of the effort to protect the ongoing, in that case insufficient processing, of visual motion from disturbing signals via the inactivation of early visual cortex. Our results also suggest that a retinotopically specific alpha localization might only be present for a limited time period.

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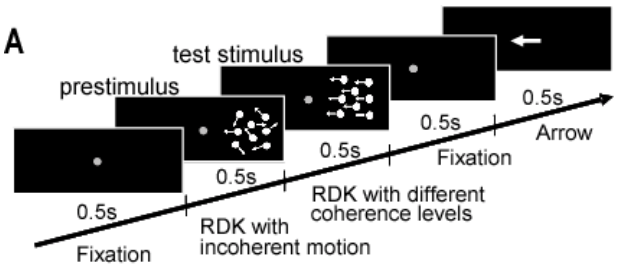
2.5 Cross-frequency coupling of brain oscillations indicates the success in visual motion discrimination

Submitted as: Händel B, Haarmeier T. Cross-frequency coupling of brain oscillations indicates the success in visual motion discrimination.

Magnetoencephalographic or electroencephalographic recordings of the human brain are characterized by ongoing rhythms that encompass a wide range of temporal and spatial scales (1-3). In the past, the functional significance of brain oscillations has usually been tested for the different frequency bands, separately. Neuronal processing, however, involves simultaneous oscillations in various frequency bands (and recent studies have suggested an oscillatory hierarchy with faster oscillations being locked to preferred phases of underlying slower waves (2-4), a functional principle applied up to the level of action potential generation. A classic example of such co-variation is the hippocampus where single cell activity is modulated along with oscillating local field potentials (LFPs; 5) and oscillations in the gamma frequency range are coupled to theta oscillations (6-8, for review see 9). Co-modulation between various oscillations and single spikes seems to be a feature prevalent in the whole cortex and not confined to the hippocampus or memory processes. In monkey sensory cortex single cell responses have been found to be coupled to preferred phases of slow wave oscillations (10: visual cortex (area V4); 4: auditory cortex) and cross-frequency coupling between slow and fast oscillations has been demonstrated in visual (monkey: 11; rabbit: 12; cat: 11, 13) as well as auditory cortex (monkey: 4). Also in humans phase locking has been observed between high gamma (80 -150 Hz) and low frequency oscillation for various behavioral tasks (auditory, visual and tactile) and over various parts of the cortex (3, 14, 15).

The functional significance of cross-frequency coupling has remained unclear. One possibility is that phase coupling is important for input selection and, more specifically, might subserve the detection of weak sensory signals (2). The reason is that the combination of fast and slow oscillations might facilitate spike generation in response to a given sensory input due to the dependency of action potential generation on even small, subthreshold electric field changes (16-19). Combination of the two oscillators might increase the magnitude of input variability so that a weak, subthreshold input might become effective in discharging a critical number of target neurons. Along this line of arguments and based on the observation that gamma-frequency modulations in visual cortex are phase-locked to the depolarization peaks of membrane potential changes in the delta frequency range, Volgushev et al. (13) speculated that phase-locking might provide visual cortex neurons with the possibility to exploit the advantages of stochastic resonance (13, 20-22) in the detection of weak visual signals.

The goal of the present study was to test this idea by resorting to a visual motion discrimination paradigm (Fig 1) which has been demonstrated recently to induce both high- (gamma, 23) and low- (delta, 24) frequency oscillations.



B

subjects	1	2	3	4	5	6	7
% correct responses	63	59	65	68	60	57	71
% motion coherence	7	6	24	11	14	14	14

Figure 1) Time course of the stimulus and stimulus specifications for the different subjects. **a** The stimulus consisted of 5 periods each lasting 500 ms. In contrast to the "prestimulus", a random dot kinematogram (RDK) consisting of incoherent motion, the following "test stimulus" involved the presentation of coherent motion the percentage of which was adjusted in each subject in order to obtain ~70% correct responses. Coherent motion was directed either to the left or to the right. Subjects had to indicate whether the motion direction of the coherently moving dots of the test stimulus was identical or opposite to the pointing direction of the arrow presented at the end of the trial. Subjects viewed the stimuli during controlled stationary fixation. **b** Percentage of correct responses and amount of motion coherence (percentage of coherently moving dots) used for stimulation are listed for each of the seven subjects separately. For the given subject motion coherence remained the same through all trials (n=420) during MEG recording. On average 63 +/-5 % of the trials were answered correctly with the mean motion coherence being 13 +/- 6%.

In order to investigate the putative role of cross-frequency coupling, we studied neuromagnetic responses obtained from human observers near their individual perceptual threshold (Fig.1, see also Suppl.) which made it possible to analyze responses for conditions that were physically the same but different in perception. As shown in Fig. 1, for each of the subjects (n=7) the percentage of correctly answered trials was higher than 50% showing that discrimination, albeit demanding, was better than chance level. Likewise importantly, differences between correct and incorrect trials did not reflect oculomotor influences (see Suppl.) but genuine differences in visual motion discrimination.

A frequency analysis was conducted in order to test for amplitude differences between correctly and incorrectly answered trials in two frequency ranges which have been observed during such tasks before: firstly, a slow frequency component in the delta range (3+/- 2Hz) was analyzed which had been shown to depend on motion coherence in a previous experiment (24) and, secondly, gamma band oscillation around 63Hz (+/- 5Hz) was investigated because this was the dominating peak in the high-frequency power spectrum of the present MEG data. For each of the two spectra the amplitudes were derived on single trial basis using a Gaussian filter. Statistical analysis comprised sensor based comparisons for the time period covering the 2,000 ms after start of incoherent motion presentation as described in detail in the Supplements. Oscillations in both the gamma and the delta band were observed over a broad range of sensors as can be seen in Fig. 2 plotting the group data. While the delta oscillation showed peak amplitudes in sensors located over bilateral occipital and temporal cortex, the gamma oscillations were more clustered around the occipital pole. As evident from Fig. 2 differences in the distribution or strength of the oscillations between correctly versus incorrectly answered trials were negligible. In fact, amplitudes did not show a significant difference between the two conditions for neither of the two spectra and for none of the 151 sensors (t-test applied on the spectral amplitudes, time interval: 500ms- 2,500ms).

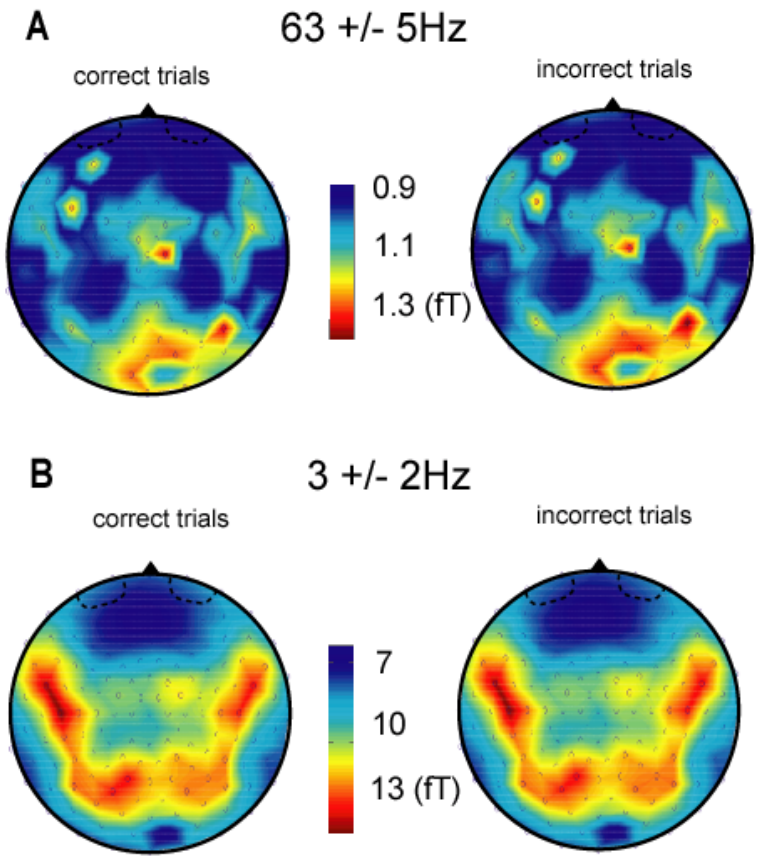


Figure 2) Spatial distribution and amplitudes of the low-frequency (3 Hz) and the high-frequency (63 Hz) signals depicted for correct and incorrect trials. **a** Amplitude values of the 63 +/- 5Hz frequency band were averaged for the group of subjects over all correctly answered trials (on the left) and all incorrectly answered trials (on the right) and projected onto a two-dimensional MEG sensor map (seen from above, nose up; time window: 500-2,500 ms after stimulus onset). **b** Amplitude values of the 3 +/- 2Hz frequency band, same convention as in a.

In contrast to the uniform pattern of results obtained for the two oscillations when analysed separately, the comparison of correct and incorrect trials revealed qualitative differences when interactions between the two spectra were considered. First of all, it is important to note that the prevalent delta oscillations and gamma amplitudes were indeed co-modulated as exemplified in Fig. 3 for a single trial.

The prevalent gamma oscillation in this trial changes its amplitude (as captured by the envelope, i.e. the Hilbert transformed curve) at a frequency closely matching the delta response of the same trial. Superposition of the delta phase and the gamma envelope reveals that high amplitudes in the gamma range tend to coincide with troughs of the delta wave. This impression was corroborated by a statistical analysis testing for significant differences in gamma amplitudes present during the peaks of the delta waves on the one hand and those recorded during delta troughs on the other hand (Fig. 4). For correct trials, the differences were locally clustered around occipital sensors with increased gamma amplitudes during the delta troughs as compared to the peaks (Fig. 4A, left map). In other sensors, these differences were virtually absent. Statistical analysis confirmed that the modulation of occipital gamma amplitude was significant as indexed by 4 neighboring sensors meeting the criterion of $p<0.018$ (Fig. 4B, see Supplements for the details of statistical analysis).

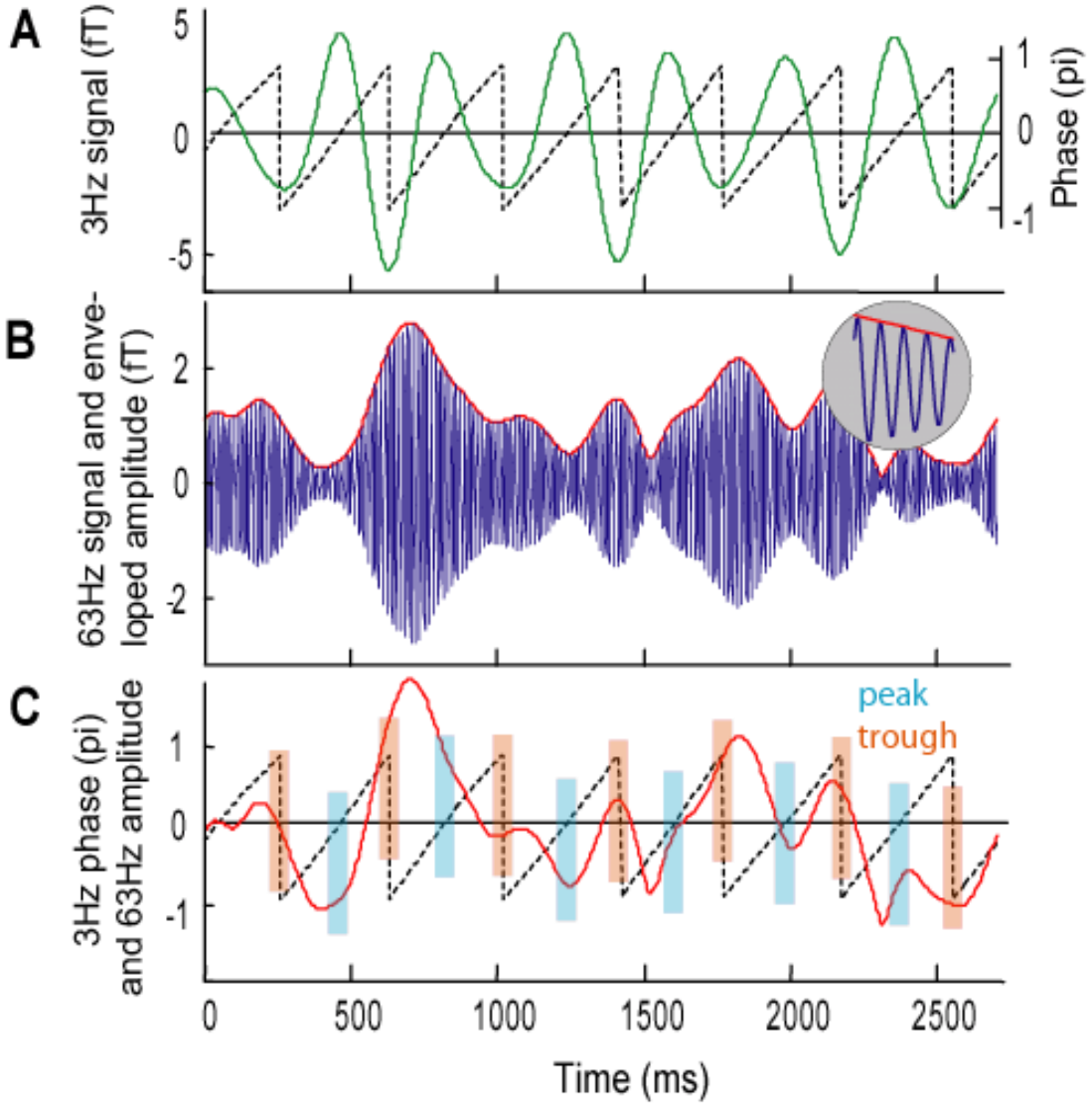


Figure 3) Relationship between gamma amplitude and delta phase shown for an exemplary trial and sensor. **a** The delta signal (3 +/-2Hz) (green solid line) and its corresponding phase (black broken line, between + pi and – pi, y-axis on the left) are plotted over the whole time of stimulus presentation. **b** The gamma oscillation of the same trial (blue solid line, the inset shows an enlargement of a short time period). The change in amplitude as identified by a Hilbert transformation is depicted in red. **c** The change in gamma amplitude (red line, same as depicted in b) and the phase of the delta oscillation (black broken line, same as in a) superimposed on each other. The y-axis shows the pi values for the phase. Amplitude values of the gamma signal are arbitrary since for clarity the curve has been shifted and magnified. Delta peaks (phase values between 0 +/- pi/12) and the corresponding gamma amplitudes are marked with blue squares, troughs (phase > pi – pi/12 & < -pi + pi/12) with red squares.

In contrast, in incorrect trials the spatial distribution of gamma amplitude modulation was rather incoherent (Fig. 4A). On the one hand, the occipital gamma modulation appeared to be weaker as compared to correct trials and on the other hand, several other sensors reaching up to frontal cortex showed modulations of the gamma amplitude. None of the modulation peaks, however, reached the level of statistical significance. Specifically, only one single sensor in the left precentral area met the statistical criterion of $p<0.018$ but did not survive correction for multiple comparison since neighboring sensors did not show the same effect (Fig. 4B).

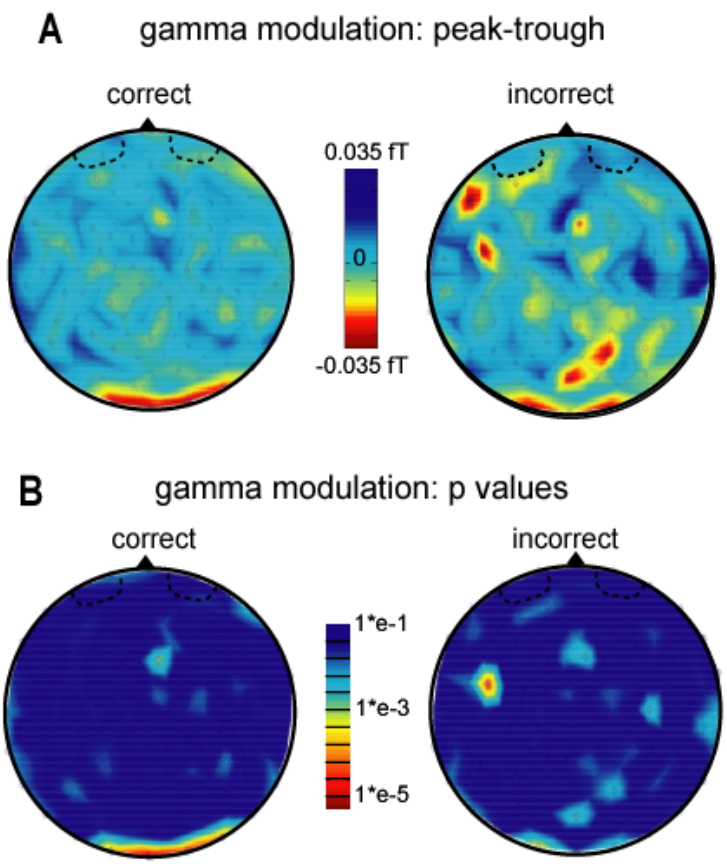


Figure 4) Spatial distribution of gamma amplitude modulation co-varying with delta phases. **a** Magnetic field map of the group difference between gamma amplitudes obtained for the delta peaks versus the delta troughs. Amplitude values were averaged for the group of subjects over all correctly answered trials (on the left) and all incorrectly answered trials (on the right) and projected onto a two-dimensional MEG sensor map (seen from above, nose up; time window: 500-2,500 ms after stimulus onset). Warm colors signify that gamma amplitudes collected during delta troughs are higher than those during delta peaks, blue colors signify the contrary. **b** Statistical probability mapping of gamma amplitude dependency on delta phase projected onto the same two-dimensional MEG sensor map shown in A. P values denoting the level of statistical significance of the gamma amplitude difference (shown in a) were calculated from t-tests and are color-coded here in order to provide a quasi-field distribution.

Albeit analyzed only occasionally, cross-frequency locking between delta and gamma oscillations is not without precedent in the literature and has been found between slow oscillations in a range of 0.1 to 10 Hz and gamma oscillations in a range of 20 to 100 Hz in animal (3, 12, 13, 25) as well as human studies (14, 15) within the visual cortex. The frequencies as well as the location, i.e. sensors over the occipital pole which exhibited cross-frequency coupling in this study, therefore, are in good agreement with previous results. Also the delta phase which the gamma modulation was locked to agrees with findings of previous studies. Our data showed an increase in amplitude of gamma oscillation during the trough of delta wave, correspondent to a phase lag of about half the delta cycle. Phase lags in former studies were ranging roughly between 1/3 pi and pi (4, 15) i.e. on the descending arm of the wave. To our knowledge, however, the present study is the first one to demonstrate a relationship between cross-frequency coupling and the success in visual discrimination. Although it is not possible to directly infer from our results whether cross-frequency coupling indicates the detection of coherent motion or entry to working memory, its dominance was related to the perceptual state of the observer. We, therefore, interpret our results in line with the hypothesis that the responsiveness of neurons to incoming sensory signals is not entirely determined by the signal itself but also by oscillatory fluctuations in the neuronal network. More specifically, the present results support the concept that coupling of different cortical oscillators provides the brain with useful noise which plays a constructive role in the detection of weak signals.

Supplements
Methods

Subjects: Seven healthy subjects, 3 males and 4 females with a mean age of 29 (+/- 2.9) years participated in this study. All subjects had normal or corrected to normal vision. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the guidelines of the local ethics committee of the medical faculty of the University of Tübingen, which approved the study.

Procedure and stimulus material: Subjects were seated upright in a magnetically shielded room (Vakuum- Schmelze, Hanau, Germany) and were instructed to sit as motionless as possible during the magnetoencephalographic (MEG) recording. Stable posture was supported by a chinrest attached to the MEG chair. The computer generated visual stimuli were rear projected onto a large translucent screen (DLP-projector (digital light processing), frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 92 cm in the magnetically shielded room. Viewing was binocular.

The visual stimulus consisted of 5 periods, each lasting 500ms (see Fig.1a) and each being observed by the subjects during controlled stationary fixation. During the first 500 ms, only a stationary red dot (diameter 10 minarc) was presented in the middle of the screen which served as the fixation target and which remained visible for a total of 2.5 s. The first 500 ms period was followed by a second one introducing a random dot kinematogram (RDK) which covered a square of 16 x 16 deg and was centred 15 deg right of the fixation point. The RDK consisted of 1500 white squares (side length = 8 arcmin, lifetime = 1000ms, dot density ~ 6dots/deg2, luminance 47cd/m2) all moving incoherently, i.e. in all possible directions with a resolution of 1 degree, at a common speed of 6deg/s. After the presentation of this first RDK, a second RDK, the “test stimulus”, started. The properties of this second RDK were identical to those described for the previous stimulus period except that a certain amount of dot elements now moved coherently in the same direction (either to the left or to the right). Specifically, the percentage of coherently moving dots was dependent on the individual threshold of the subject detected as will be described below. After a subsequent second fixation period, an arrow was presented in the middle of the screen pointing either to the left or to the right side as randomly chosen by the stimulus generator. Subjects were instructed to keep fixation as accurately as possible during the whole trial and to indicate by lifting their right or left index finger whether the motion direction of the dots of the test stimulus was identical (right index finger) or opposite (left index finger) to the pointing direction of the arrow. Subjects were instructed to guess if they were not sure about the direction seen (forced choice). Finger movements were detected using a light barrier. The individual measurement consisted of 420 single trials. The individual threshold was identified beforehand by using a set of trials modulated by a staircase procedure in which the coherence level was varied until 70% of all trials were answered correctly. This coherence level was then used for further stimulation.

During all experiments, eye movements were monitored using a homemade video system taking the pupil’s center as measure of eye position. Recordings were stored at a sampling rate of 50 Hz and analyzed offline in order to assess the quality of fixation. In particular, oculomotor parameters like eye velocity, eye position and number and amplitude of saccades

were tested for differences between correctly and incorrectly answered trials using t-statistics. None of the different measures showed statistically significant differences.

Recording of the MEG signals: Neuromagnetic activity was recorded using a whole-head MEG system (CTF Inc., Vancouver, Canada) comprising 151 first-order magnetic gradiometers. The signals were sampled at a rate of 625 Hz. Recording epochs lasted from stimulus onset to arrow offset plus 200ms, leaving 2,700ms of recording time for each trial. The subject's head position was determined at the beginning and at the end of each recording session by means of localization coils fixed to the nasion and preauricular positions to ensure that head movements did not exceed channel separation. Trials showing movement artifacts were detected by visual inspection and excluded. Baseline correction was performed by subtracting the mean of the whole stimulus period for each channel, separately.

Frequency analysis: Spectral analyses were performed on two frequency bands. The frequency of the slow wave was chosen on the basis of a previous experiment which had shown a strong prevalence of 3+/- 2Hz oscillations for the same motion paradigm (Händel et al., 2007, Cer Cortex). The gamma band around 63Hz (+/- 5Hz) was chosen because of a pronounced peak in the power spectrum. MEG recordings were Gaussian filtered for the two frequency bands (i.e. 3+/-2 Hz and 63+/-5 Hz, respectively) on a single trial basis. Only the time period from 500 ms to 2,500 ms, i.e. from the start of the incoherent motion presentation until the end of the arrow presentation was analyzed. Amplitude values were compared between correct and incorrect trials for the gamma and delta band by using a t-test across the Hilbert transformed amplitude values.

Analysis of gamma amplitude during delta peaks vs. delta troughs: To analyze cross-frequency coupling we tested in a first approach if the amplitudes of the gamma oscillation would be different during the peaks of the delta wave compared to the delta troughs (see Fig. 3, Canolty et al., 2006, Science). To this end we extracted for each trial separately the Hilbert modulated amplitude values of the gamma band for those points in time for which the delta phase of the given trial would be within a range of 0 +/- pi/12 (covering the peak in the delta wave) or would meet the trough criterion (phase > pi – pi/12 & < -pi + pi/12). The only requirement for a given single trial to be accepted was that at least one full circle of delta had to be present (i.e. 34 samples [=55.5ms] had to fulfill peak and trough criteria, respectively, as defined before). Gamma amplitude values were now averaged separately for the peaks and troughs leaving us with one (mean) peak and one (mean) trough value for each trial, each sensor and each subject. Trials were further sorted for correctly answered trials and incorrectly answered ones. Since the percentage of correctly answered trials was higher than 50% (compare Fig. 1B), we matched the number of trials using a randomization process. A group statistic (t-test over 7 subjects) was now calculated for each sensor comparing the peak values with the trough values within each group of trials (correct and incorrect trials), separately. The p levels taken to be significant were adjusted by means of a Bonferroni correction given that the p values of two adjacent sensors had to be significant (p_corrected= sqrt(0.05/ 151 sensors) = 0.018).

To exclude the possibility that movement artefacts influenced the results we computed the identical analysis as before but now using 120 +/-10 Hz as filter frequency, a frequency often found to be prevalent during movements. No significant difference between peak and trough was found and no neighbouring sensor showed a sign value below 0.1.

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2.6 Gamma oscillations underlying the visual motion after-effect

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Introduction

Since the report of high frequency oscillation in the octopus retina (Fröhlich, 1913) a lot of work has been conducted in an attempt to unravel the neuronal basis and the functional role of the so called gamma oscillations. Besides the differentiation in at least three different types, i.e. evoked (phase locked), induced (non-phase locked) and base line gamma activity (for review see Bertand et al., 2000; Müller et al., 2000) several hypothesis have tried to explain its functionality. One influential idea has been the suggestion that the synchronization of regional gamma oscillations may underlie the formation of a coherent percept, based on elementary stimulus features, assumed to be represented in distinct cortical areas, thereby needed to be bound (the "binding problem", see Singer, 1999; Gray, 1999 for review).

Increasing evidence indeed suggests that neuronal gamma band (40–100 Hz) synchronization is a fundamental process involved in several important brain functions, including visual feature binding (Eckhorn et al., 1988; Gray et al., 1989; Tallon-Baudry et al., 1996; Tallon-Baudry et al., 1997; Lutzenberger et al., 1995; Freunberger et al., 2007; Kaiser et al., 2004a; Herrmann et al., 1999; Müller et al., 1996; Krishnan et al., 2005), bistable percept (Rodriguez et al., 1999; Lachaux et al., 2005; Keil et al., 1999; Müller et al., 2000; Basar et al., 1996), attentional stimulus selection (Lakatos et al., 2004; Fries et al., 2001; Sokolov et al., 1999; Gruber et al., 1999; Tallon-Baudry et al., 2005), working memory (Tallon-Baudry et al., 1998; Lutzenberger et al., 2002) and associative learning (Miltner et al., 1999). For overview see Tallon-Baudry (2003), Basar (1996), Engel (2001), Kaiser (2004b) and Kahana (2006).

Up to now, the involvement of gamma oscillations in visual perception has, with two exceptions, been explored in humans by using stimuli in which changes of stimulus features underlie changes in perception. Only two groups used perceptually ambiguous stimuli. Besides an early study, which revealed increased gamma band activity (GBA) selectively during the reversal of an ambiguous motion percept over the whole cortex (Basar et al., 1996), a later study could show that horizontal motion involving perceived movement from the left to the right visual hemifield induced synchronisation between occipital sensors lying over the left and right hemisphere. This synchronisation was not observed if the ambiguous motion was observed as moving vertically in only one hemifield (Rose, et al., 2005). However, both groups compared two different but equally valid perceptual states rather than a state characterized by the presence of a percept vs. a state in which the same percept was absent, although the visual stimulus was still available. We therefore asked if we could detect a difference in GBA for a situation in which a percept was present or absent independent of the visual input. To this end we used the motion after-effect (MAE) which describes illusory motion perception due to prolonged exposure to strong visual motion in one direction. A

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second important question we wanted to answer was if GBA representing perceptual states would be visible over the sites of primary visual processing or rather at a higher level.
Efforts to locate the structural and the physiological basis of the MAE as yet have relied on single-unit recordings from the visual cortex of monkeys (Petersen et al., 1985; Kohn et al., 2003) and fMRI (Tootell et al., 1995; He et al., 1998; Culham et al., 1999; Taylor et al., 2000) and PET (Hautzel et al., 2001) studies of the human brain, jointly singling out area MT and neighbouring cortex as the major substrate of the MAE. Additional evidence for a role of human MT+ comes from studies using repetitive transcranial magnetic stimulation (TMS) which could show that TMS of human MT+ disrupted the perception of the MAE (Theoret et al., 2002).
In an attempt to capture high frequency oscillations possibly underlying the MAE we used magnetoencephalography (MEG). We found increased GBA over parietooccipital sensors and an increased strength in dipoles located near the putative location of human area MT+ for the MAE compared to the no-MAE condition. An additional focus of GBA whose signal amplitude correlated with the size of the MAE could not be located to a specific region. Possible sources of this second focus will be discussed.

Methods

Subjects: Eight subjects (two females, mean age 28.0 years) in experiment 1 and 9 subjects in experiment 2 (four females, mean age 28.0 years) gave their informed and written consent to participate in the study after having had the experimental protocol explained to them. All of the subjects had normal or corrected to normal vision, were right-handed and had no history of neurological disease. The experimental protocol of the study had been approved by the ethics committee of the Tübingen Medical Faculty.
Stimuli: Stimuli were rear projected onto a large translucent screen (DLP Projector, frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 92 cm in a magnetically shielded room. Viewing was binocular. A red spot (diameter 10 min of arc), presented in the middle of the screen, served as a gaze fixation target during the whole trial. The visual motion stimuli were projected unilaterally into the right (experiment 1) and the left (experiment 2) visual hemifield, respectively, at an eccentricity of 12.5 deg (fixation spot to middle of the motion stimulus) on the horizontal meridian. Stimuli subtended a visual angle of 9 x 9 deg and consisted of 300 white dots (diameter: 15 min arc; luminance: 65 cd/m2; individual life-time: 200 ms) which were randomly plotted on a dark background. Dots that left the stimulus aperture were re-plotted in randomly chosen positions within the aperture. Each experimental trial (see Fig. 1) began with a blank interval (duration 0.5 s), in which only the central fixation spot was visible. This interval was followed by a priming phase lasting 5.0 seconds during which a random dot pattern (RDP) was presented (Fig. 1). Different for two conditions applied, the 300 dot elements would either move coherently downward (MAE condition) or would move in individually varying directions (motion-balanced) drawn from a distribution of directions spanning 360 degrees (no-MAE condition). After a subsequent second blank interval (0.4 s) the test phase (duration: 0.5 s) started. In this test phase, again a RDP was presented in which the dots moved in individually varying directions as described for the priming phase of the no-MAE condition. When presented in isolation, this motion-balanced RDP lacked global motion and appeared as a flickering, globally stationary pattern. However,

when preceded by a coherent RDP as in the MAE condition it seemed to move upward, i.e. in a direction opposite to that of the priming stimulus due to the motion after-effect induced. At the end of each trial, subjects were required to indicate their perceived direction of global motion of the second RDP by lifting their index finger (perception of downward motion) or middle finger (perception of upward motion) of their right hand (experiment 1 and 2). Trials with coherent and incoherent visual motion during the priming phase (MAE versus no-MAE condition) were presented in two subsequent blocks. The sequence of these two blocks was pseudo-randomized across subjects.

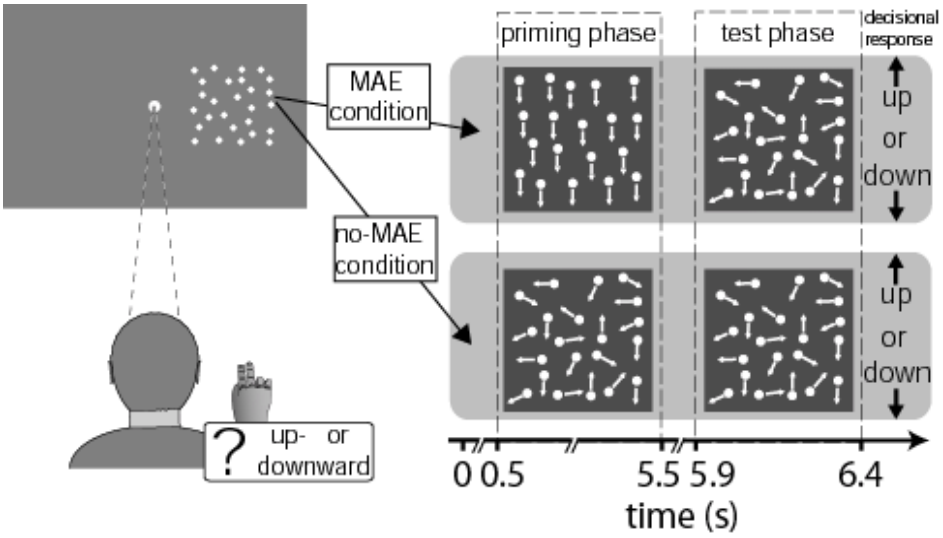

Figure 1) Experimental paradigm. Sequence of events in an experimental trial. The random dot pattern (RDP) was presented always right of the fixation spot in experiment 1 and left of the fixation spot in experiment 2. Dashed lines indicate the time of presentation of the RDP. In the priming phase, downward moving coherent RDP was presented in the MAE condition, whereas, alternatively, a motion-balanced RDP in which dots moved in random directions was seen used in the no-MAE condition. In the subsequent test phase, a *RDP* was presented in both conditions, in which the individual dots moved in random directions. Whereas in MEG trials the net motion was balanced, in psychophysical trials (not shown here) a vertical motion component of varying size was added in order to titrate the size of the MAE. Subjects reported the perceived direction (up- or downward) of the global motion of the RDP in the test phase by lifting the middle finger (motion upward) or the index finger (motion downward) of their right hand (two-alternative choice).

Trials as described so far were shown in 75% of all presentations and were termed MEG trials because only they contributed to the MEG records. In the remaining 25% of trials, called psychophysical trials, there was a change in the stimulus concerning its test phase. In the MEG trials the test phase lacked coherent motion as described above. However, in the psychophysical trials the motion-balanced RDP underlying the test phase stimuli was biased by introducing a constant amount of vertical motion added vectorially to all dot elements. The movement of each individual dot was given by summing the vertical bias vector, which was the same for all dots, and the individual dot velocity vector underlying the unbiased motion-balanced RDP. If the size of the biased motion vector corresponded to the size of the oppositely directed MAE, the physical motion and the illusory motion annihilated each other, rendering the biased motion-balanced RDP perceptually stationary. In order to determine the

size of the vertical (downward) motion bias needed to render the stimulus stationary (velocity of subjective stationarity), its size was varied from psychophysical trial to psychophysical trial by a PEST staircase procedure (Taylor and Creelman, 1967; Lieberman and Pentland, 1982). The velocity of subjective stationarity at which subjects will guess the direction of global motion as indicated by equal numbers of upward and downward decisions was determined by means of a probit analysis (McKee et al., 1985) with subsequent chi-square goodness-of-fit tests performed on the responses obtained for psychophysical trials. The bias motion vector at the velocity of subjective stationarity is equal in size but opposite in direction to the MAE and may therefore serve as an operational measure of the MAE. Given the fact that the psychophysical trials were presented randomly interleaved with the MEG-trials, we assumed that this measure of the MAE based on psychophysical trials was representative of the MAE in MEG trials as well. We felt that titrating the size of the MAE prompted by the presentation of the incoherently moving dots quantitatively in this way, was preferable to asking subjects simply whether a MAE is present or absent when viewing a stationary test pattern and to measure the duration of the percept as has been custom in previous studies (e.g. Culham et al., 1999; Taylor et al., 2000, Hautzel et al., 2001). A full block of trials comprised 120 MEG trials, independent of the actual number of psychophysical trials, of either the MAE or no-MAE condition.

Recording of eye movements: Subjects were instructed to fixate the central fixation spot as accurately as possible while avoiding head movements. Head movements were further reduced by employing a bite bar, attached to the MEG chair. During all experiments, eye movements were monitored using a 50 Hz home made video based eyetracker. The means of eye velocity and the frequency of saccades during background presentation were calculated off-line for each individual subject for the different classes of trials. Only trials accompanied by fixation within a 3° fixation window were accepted for further analysis.

MEG recordings: MEG was recorded using a whole-head system (CTF Inc. Vancouver, Canada) comprising 151 first-order magnetic gradiometers. The signals were sampled at a rate of 625 Hz with a 200 Hz anti-aliasing filter. The MEG records were resampled offline to 312.5 Hz. One of the sensors located over the left frontal cortex (LF13) had to be excluded from later analysis because of a technical dysfunction during recordings. Fixation point onset at the beginning of each trial started the sampling. The total sampling epoch per trial was 6400 ms and lasted up to the end of the test phase. Subjects´ head position was monitored using a set of three magnetic head localization coils attached to the nasion and two preauricular reference points. Head position measurements were conducted at the beginning and at the end of each experimental block (120 MEG trials) in order to verify the stability of head orientation. Due to technical problem 2 sensors (LT15, RP11) had to be excluded.

Analysis of the global field power: To investigate the spectral, temporal and spatial aspects of the MEG activity associated with the percept of MAE, the following approaches were used. In a first attempt to search for MEG activity reflecting the MAE, we analyzed the global field power (GFP). In order to obtain the GFP, the MEG recordings were first of all baseline corrected with respect to an interval ranging from -100 to 0 ms before test phase onset which corresponds to the 100 ms blank period between priming phase and test phase. The recordings were then digitally low-pass filtered at 40 Hz and averaged over trials for the two conditions (i.e. MAE and no-MAE) and each subject. Based on these averages, the global

field power was calculated for the MAE and no-MAE condition as the root of the mean squared magnetic fields (RMS) of all sensors (149 of 151) for each sample and for each subject.

Dipole analysis: An equivalent current dipole (ECD) model was calculated using the averaged magnetic field independent of the condition for each subject separately over the first 250 ms of the test phase of the trial. A representative individual spherical head model was used and the corresponding ECDs were determined by a least-square minimization procedure based on running standard BESA and CTF software. For each subject the individual dipole positions were mapped into the Talairach stereotactic standard space. In a second step neuromagnetic activity averaged separately over the two conditions (MAE and no-MAE) was modelled using the previously obtained dipole locations. Dipoles were determined as previously described but in order to elucidate the temporal dynamic, dipole strength was extracted for the whole time period of the test phase. ECD moments obtained for the two conditions were then subtracted and time periods in which the difference exceeded the baseline noise level (3 times STD) calculated at the 50 ms pre-stimulus interval were identified. In addition a regression was calculated between the difference of the mean dipole moment of the first 250 ms of the test phase for the MAE and the no-MAE condition and the difference of the percept in the two conditions. This regression was carried out separately for the two dipoles considered and showed no significant effect ($p > 0.05$).

Spectral analysis: Spectral analysis was carried out in order to identify high frequency oscillations (40-100 Hz) connected to the MAE. To this end, the MEG signals recorded during the test phase were analyzed on single trial basis. Selecting this time window of 500 ms resulted in 156 samples (sampling rate 312.5 Hz), which were zero-padded to obtain 256 points. To these data points a Welch window was applied and a Fast Fourier transformation (frequency resolution: 1.221 Hz) was conducted. The square roots of the obtained power values were then averaged across trials for each frequency bin, sensor, experimental condition and subject. Differences in power between the MAE and no-MAE condition were assessed for each sensor and each frequency bin (within a range from 40 Hz to 100 Hz) by applying a t-test. In order to correct for multiple comparison, a statistical sensor analysis (SSA) was performed, as described in detail further below.

We not only wanted to analyse the group differences between conditions but also if the percept of the MAE would be reflected in the MEG signal. We therefore searched for significant linear correlations between the perceptual differences between the MAE and the no-MAE condition of the individuals and the corresponding individual differences in spectral power for each sensor and for each frequency bin. The correlation coefficients obtained from linear regressions were transformed to t-values and their significance was tested again by the statistical sensor analysis conducted as follows.

Statistical Sensor Analysis (SSA) was based on randomisation tests (Blair and Karniski, 1993; Noreen, 1989; Kaiser et al., 2006) and included corrections both for multiple comparisons and for possible correlations between data from neighbouring frequency bins and sensors. In general, permutation analysis estimates the significance of actual test-values by applying the identical tests to simulated data, obtained by permutation of the actual observations. The significance criterion is estimated on the basis of the permuted data in such a manner that the critical test-value is the one for which 5% of the test-values are greater. If the test-value of the

original data lies above this critical test-value the statistical test is considered significant. One concern, however was, that differences between conditions restricted to one sensor or one frequency bin only are taken as significant even though such events are extremely unlikely, especially as we take quite small frequency bins into account (1.2 Hz). To exclude this possibility, we additionally further demanded that always two neighbouring frequency bins or sensors had to show a significant effect. To this end we used a slightly altered method as has been described previously by Lutzenberger et al. in 2002. To demand two neighbouring events to be significant at the same time is a quite common approach (e.g. Fell et al., 2001; Trautner et al., 2006).

In a first step, test-specific statistics (i.e. t-test or linear correlation, respectively) were evaluated for each sensor (total = 150 sensors) and each frequency bin (width 1.221Hz, band of 40-100Hz, total = 48) resulting in a first distribution of test-values. To ensure that tests for two neighbouring frequency bins and sensors were significant, a new distribution of minimal test-values was determined for all pairs of neighbouring frequency bins and sensors by taking only the smaller one of the neighbours into account. Now P0.05 was determined as the p-value corresponding to the test-value from the new distribution for which 5% of the observed minimal test-values were greater. In the case of highly correlated data, P0.05 would be ≤ 0.05, whereas for highly independent data, P0.05 would be >0.05 (Kaiser et al., 2000, Lutzenberger et al., 2002).

In a second step, the corresponding distribution of maximal test-values was calculated for the permuted data sets, taking only the larger test-value of all pairs of neighbouring frequency bins and sensors into account. Based on this distribution the critical test value tcrit was defined as the test value where P0.05 x number of permutations of the obtained maximal test-values were greater. The obtained critical t value tcrit was then applied as criterion of significance to the observed original data (Lutzenberger et al., 2002).

Permutations were conducted as follows. For the group statistics (t-test), data from all sensors and frequency bins were exchanged between the two experimental conditions (MAE and no-MAE conditions) for one or several subjects chosen by chance (number of permutations = 2n; with n=8 for experiment 1; n=9 for experiment 2). For the correlation analysis data from all sensors and all frequency bins were permuted across individuals resulting in a new pairing between perceptual data (difference in MAE between conditions) and brain activity (difference in spectral amplitude between conditions). The number of permutations made in that way was 8000; each of those was randomly selected out of n! (n= number of subjects) its possible number.

Time course analysis: Having identified those MEG signals showing a significant effect in the group and correlation analysis we tried to capture the time course of these. To this end, the signal at the time of interest (test phase) was padded to 312 samples by mirroring the first 16 samples of the signal to the temporal interval prior to the signal and the final 16 samples of the signal were mirrored to the temporal interval subsequent to the signal. The mirrored portions now were multiplied with cosine windows, centred either on the first sample of the signal (for the first padded portion) or centred on the last sample (for the final padded portion). The so treated signal was now bandpass filtered using a Gaussian curve-shaped Gabor filter (width: 2.5 Hz) centred on the frequency range for which the preceding analysis had yielded significant effects. The filtered data were now amplitude-demodulated by means

of a Hilbert transformation (Clochon et al., 1996). The resulting representation of the time course of the amplitude in the filtered frequency band was used to investigate the time course of the previously found effects, i.e. group differences between conditions and the correlation of the spectral amplitude with the MAE of the individual subject, respectively. For the first mentioned, the amplitude values, averaged across trials in each subject, were compared between conditions for every point in time using a running t-test. For the second effect mentioned, a correlation between the difference in perceived MAE and the difference in spectral amplitude between the two conditions was evaluated over the subjects for each time point by a running linear regression. SSA was used as described above to test for significance taking the correlation between consecutive time points into account.

Results

For the eight subjects participating in experiment 1, the mean MAE in the MAE condition amounted to 2.9°/s (Fig. 2A), i.e. corresponding to the perception of upward motion while watching the motion balanced RDP. Surprisingly, the mean measured MAE in the absence of a priming stimulus deviated significantly from zero as well (1.6°/s). A psychophysically measured MAE in the absence of induced motion is likely to reflect a response bias for upward motion. Hence, it is the significant increase in the size of the mean MAE by 1.3°/s (one-sided paired t-test, $p<0.0001$) obtained for the MAE condition compared to the no-MAE condition that reflects the true size of the MAE. Importantly, this perceptual difference was not paralleled by any differences in the quality of fixation as indicated by the fact that the residual eye velocities were the same during the presentation of the test stimulus in the two conditions (running paired t-tests, for all samples of the test phase; $p > 0.05$). Moreover, we did not find a significant correlation between the individual differences in the size of the MAE in the two conditions and the individual quality of fixation as assessed by calculating the difference in mean retinal image velocity between conditions ($p>0.05$).

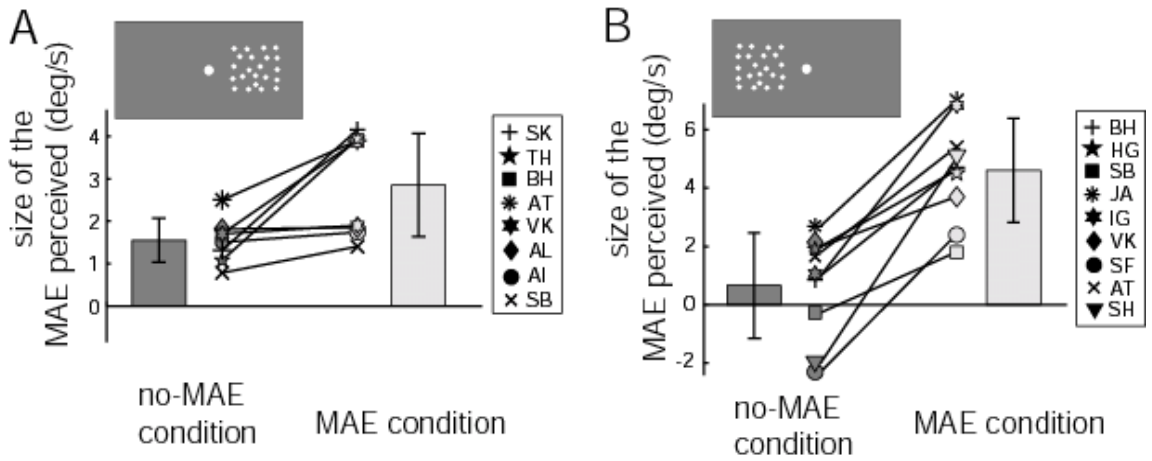

Figure 2) Perceptual data. ***A,*** Size of the MAE perceived in the MEG trials of the first experiment, in which the RDP was presented right of the fixation spot. The different symbols indicate individual subjects; the bars give means and standard deviations. Results are shown for the no-MAE condition (defined by the priming stimulus lacking consistent downward motion) and the MAE condition (with the priming stimulus moving coherently in downward direction). Positive velocities correspond to an upward direction of the MAE perceived. ***B,*** Size of the MAE in the second experiment, in which the RDP was presented left of the fixation spot, same conventions as in A.

In order to determine those MEG components which differed significantly between the two conditions (MAE versus no-MAE) during the presentation of the MEG-stimulus we first looked at the global field power (GFP). The upper 3 panels of Fig. 3A show the group averages of evoked neuromagnetic responses (8 subjects, 151 sensors overlaid) as a function of time for the two conditions and their difference. Time during the presentation of RDP in the test phase of the trial (500 ms, grey area) is shown as well as 50 ms prior to its onset. The lower panel depicts the mean global field power signals, i.e. the root mean squared neuromagnetic responses across all channels, averaged over all subjects for the MAE (black) and the no-MAE condition (grey).

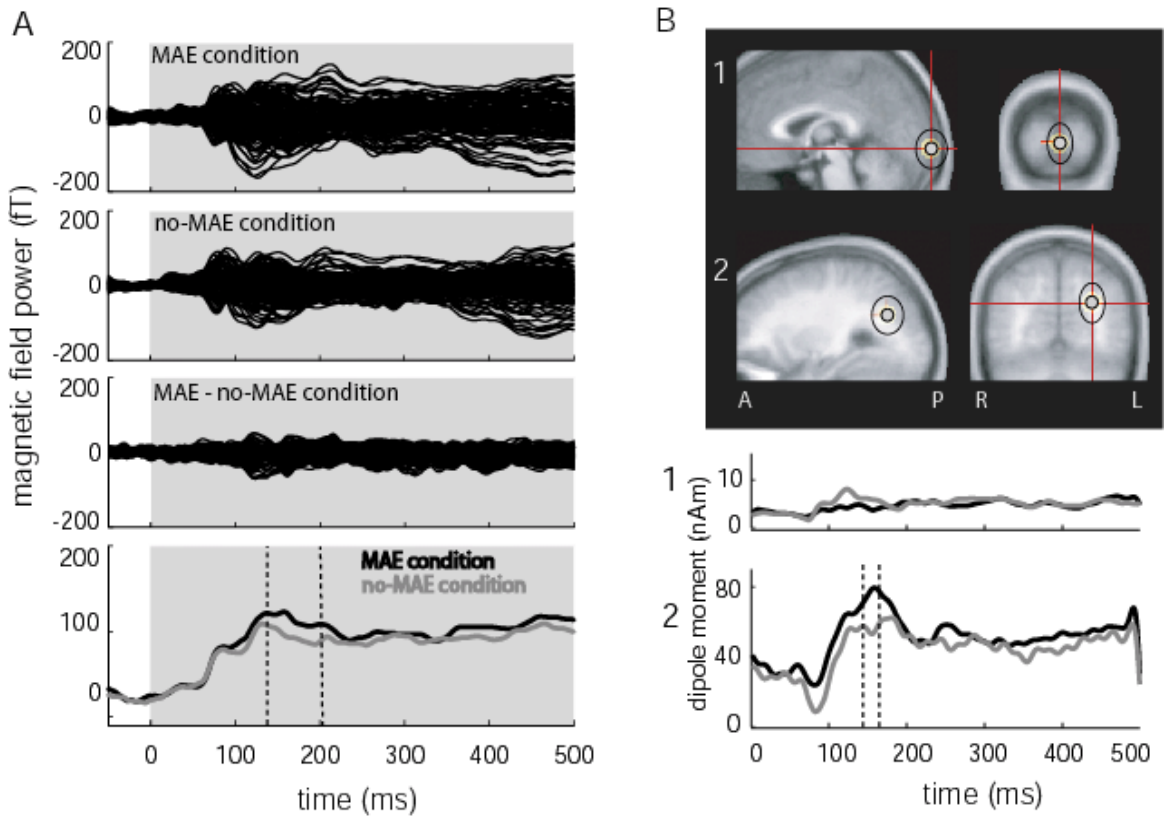

Figure 3) Neuromagnetic responses obtained under the MAE and no-MAE condition; group data (experiment 1). **A,** Upper three panels: group averages of evoked neuromagnetic responses (8 subjects, 149 sensors overlain) shown as a function of time for two conditions and their difference; MAE test phase (500 ms) is marked in grey. The fourth panel shows the mean global field power signals, i.e. the root mean squared neuromagetic responses across all channels, averaged over all subjects for the MAE (black) and no-MAE condition (grey). The time period in which the difference between the two conditions surpassed the noise level measured during the 50ms pre-stimulus period by at least 3STD is marked by broken lines (140-200 ms after stimulus onset). **B,** Dipole locations (open circles) modelling the magnetic field across the period of interest (first 250 ms of the RDP presentation) calculated from the data averaged over the two conditions for each subject separately (L: left; R: right; A: anterior; P: posterior). The broken circles mark the STD of the localisation between subjects. The upper lineplot depicts dipole moments over time for dipole 1 (upper picture) averaged over subjects. Grey lines depict dipole moments over time obtained from trials of the no-MAE condition and black lines from the MAE condition. Dipole 2, depicted in the lower lineplot (with identical convention) shows for the time period between 144 -166 ms a difference between conditions which surpassed the noise level measured during the 50ms pre-stimulus period by at least 3STD as indicated with two black dotted lines.

The first time period in which the difference between the two conditions surpassed the noise level by at least 3STD is marked by broken lines (140-200 ms after stimulus onset). During this time the global field power was increased for the MAE condition. In order to localize this effect, we fitted ECDs to the magnetic field as described in the methods and which explained for all subjects on average 66% (±11.9 %) of the overall variance.

Dipole locations modelling the magnetic field across the period of interest (250 ms of the RDP presentation) as calculated for both conditions are shown in Fig. 3B plotted onto a normalized brain (L: left; R: right; A: anterior; P: posterior). Open circles show the dipole positions, one lying at the occipital pole presumably in area V1 (upper panel, mean talairach coordinates: x= -4.07 ±10.38; y=-75.16± 12.86; z=6.13 ±17.03), the second one lying in the lateral hemisphere contralateral to the side of visual stimulation (mean talairach coordinates: x= -31.74 ±10.98; y= -63.08 ±13.97; z= 24.88 ±16.59), in a region most probably comprising area MT+. The lower part of Fig. 3B plots the group mean dipole moment as function of time for the two dipoles considered, separately for the two perceptual conditions. The upper lineplot (1) depicts the moments of the occipital dipole with the grey line representing trials of the no-MAE condition and black lines of the MAE condition. One can see that there is no significant difference (as defined by exceeding 3 STD of the difference measured during the 50ms pre-stimulus time period) for the occipital dipole between MAE and no-MAE condition. However, the parietooccipital dipole depicted in the lower lineplot (2) of Fig. 3B (with identical convention) shows a significant difference for the time period between 144 -166 ms demarcated by the two black dotted lines. Within this period of time, the dipole moment is larger for the MAE condition than for the no-MAE condition.

Using statistical sensor analysis (SSA; see Methods), we tried to determine those MEG sensors which picked up gamma-band activity (GBA) differing significantly for the group of subjects between the two conditions (MAE versus no-MAE) during the presentation of the MEG-stimulus. SSA revealed an increase in GBA in the MAE condition relative to the no-MAE condition for sensors lying above left lateral parietal cortex (LLPC), i.e. contralateral to the side of the visual field stimulated. As can be drawn from Fig. 4A, which depicts the p-values of this group difference for all sensors, this effect reached the level of statistical significance ($p<0.05$ after correction for multiple comparison) in one sensor located immediately adjacent to the intraparietal sulcus (sensor LP23). This increase in GBA activation was confined to a narrow frequency band of 69–71 Hz (Fig. 4B). In a second step, we correlated individual differences in the size of the MAE between the two conditions with the individual differences in spectral power for each sensor and each frequency in the range of 40 to 100 Hz. As shown in Fig. 4C, the sensors that showed a linear correlation between the individual amount of change in motion perception and the individual difference in spectral power were clustered over the most inferior and posterior parts of the brain located ipsilateral to the visual field stimulated. Again, this main effect was confined to a narrow band of GBA (94 +/- 2.5 Hz; Fig. 4D) and survived correction for multiple comparisons in one of the sensors (sensor R041). For this sensor the linear correlation between the change in motion perception and change in spectral power was rather striking as reflected by a correlation coefficient r of –0.965 (Fig. 3F). The possible concern that amplitude differences were caused by individual differences in head size, location or any kind of head or neck movements can be dispelled by the fact that such changes must be expected in a quite broad frequency band.

However, the effect described above as well as those that will be described below are restricted to a very narrow frequency band (see again Fig. 4B and D).

Next, in order to assess the time course of MAE associated neuromagnetic activity in the parietal sensors, we calculated the probability of finding higher GBA in the MAE condition as compared to the no-MAE condition in the frequency range of 70 ± 2.5 Hz for all time bins of 3.2 ms duration during the presentation of the MEG-stimulus. The analysis was confined to the sensor above the LLPC and the frequency range that had demonstrated significantly higher GBA for the MAE (marked in Fig. 4A), when the test phase as a whole had been considered.

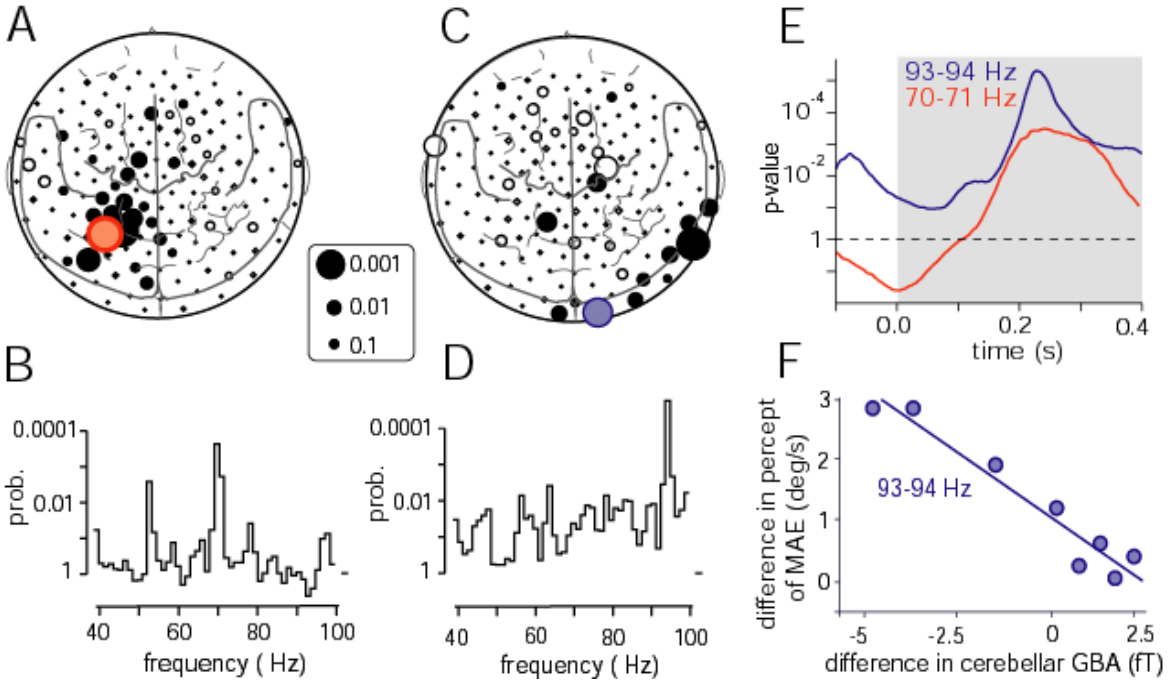

Figure 4) MEG correlates of the MAE (experiment 1). ***A,*** Probabilities of spectral amplitude differences in GBA (70 ± 2.5 Hz) observed for the group of subjects between the MAE condition and the no-MAE condition during observation of the motion noise stimulus. The size of the sensors plotted over a flattened map of the schematic brain depicts the level of statistical significance (uncorrected), the larger the sensors the smaller the p-value. Filled circles mark those sensors which showed an increase in amplitude in the MAE condition compared to the no-MAE condition, open circles mark sensors with opposite dependencies. The red colored circle marks a parietal sensor (LP23) which shows a significant increase in GBA in the MAE condition ($p<0.05$, corrected for multiple comparison). ***B,*** Frequency distribution of the p-values depicting the level of statistical significance of the difference of MEG activity between the MAE and no-MAE condition recorded from sensor LP23 (marked in red color in A). ***C,*** Probabilities of the correlation between the MAE and GBA mapped across all sensors of the MEG sensor array (same conventions as in A). Filled circles mark those sensors which show a negative correlation between the individual change in spectral GBA amplitude (94 ± 2.5 Hz) and the individual change in MAE. The blue circle marks a sensor (RO41) with a significant correlation ($p<0.05$, corrected for multiple comparison). ***D,*** Frequency distribution of the p-values depicting the level of statistical significance of the correlation between GBA recorded from sensor RO41 (marked in blue color in B) and the MAE. ***E,*** Time courses of GBA effects for the sensors that showed significant effects. The curves depict the results of the statistical analysis, i.e., p values for time points between 100 ms before and 400 ms after test phase onset. The curves are displayed in the same colors as the corresponding sensors. P-values below the dashed line correspond to t-values and regression coefficients, respectively, favouring the alternative hypothesis. ***F,*** The individual difference in the size of the GBA in the range of 94± 2.5 Hz recorded from sensor RO41 for the MAE condition as compared to the non-MAE condition shows a significant correlation with the individual difference in the size of the MAE for the two conditions (8 subjects). The negative regression indicates that lesser cerebellar activity corresponded to a higher MAE.

By the same token, in order to describe the time course of the percept-related neuromagnetic activity seen by the right posterior inferior sensor, we calculated the probability of the correlation between the percept and the spectral power for all time bins of 3.2 ms during the presentation of the MEG- stimulus. The analysis was confined to the frequency range of 94 ± 2.5, which had yielded a significant correlation between percept and oscillatory activity as calculated for the overall test phase. Fig. 4E compares the probabilities of the statistical measures for the LLPC and the RCH as a function of time. Both LLPC and RCH related p-values reached their respective maxima around 230 ms after the onset of the MEG-stimulus. Actually, the correlation for the RCH (Fig. 4E) started to become significant even before the onset of the test stimulus (80 ms before stimulus onset, $p<0.05$ corrected for multiple comparisons).

The validity of the findings obtained in this first experiment was tested by running a second experiment, based on nine subjects. In this second experiment all visual stimuli were flipped to the opposite side of the visual field without changing any other feature of the first experiment. In this second experiment, the mean difference of the MAE between the two conditions amounted to 3.8°/s (Fig. 2B). The overall pattern of neuromagnetic responses obtained in this second experiment was similar to the one obtained in experiment 1. The main difference was that all responses changed sides.

As in experiment 1, the GFP showed a first significant increase (3STD above noise level, marked with broken lines) in activity elicited by the MAE compared to the no-MAE condition, however, shorter in duration and at a slightly later latency (196- 212 ms) as in experiment 1 (see Fig. 5A, lower panel). The upper 3 panels of Fig. 5A show the group averages of evoked neuromagnetic responses (9 subjects, 151 sensors overlaid) as a function of time for two conditions and their difference. ECDs were fitted to the magnetic field as described in the methods (5 subjects with a mean explained variance of 59 ±13.5%) and dipole locations (open circles) are shown in Fig. 5B plotted onto a normalized brain (L: left; R: right; A: anterior; P: posterior). As in experiment 1, we found one dipole lying at the occipital pole, presumably in area V1 (upper panel, mean talairach coordinates: x= -1.3 ±21.45; y= -95.49 ±20.35; z= -2.95 ±17.08) and a second dipole, contralateral to the visually stimulated side, more lateral (mean talairach coordinates: x= -33.93 ±9.53; y= -59.04 ±15.45; z= 15.8 ±16.35) close to the putative location of area MT+. The group mean dipole moments are plotted as functions of time separately for the two conditions (MAE = black and no-MAE = grey) in Fig. 5B (2 lowest panels). The upper lineplot (1) depicts dipole moments for the occipital dipole. It exhibits no significant difference between conditions (as defined by exceeding 3 STD of the difference measured during the 50ms pre-stimulus time period). However, the moment of the second, temporooccipital dipole, depicted in the lower lineplot of Fig. 5B, showed a significantly increased strength for the MAE condition for a short time period between 200- 212 ms (demarcated by broken lines). However, these results are based only on those subjects whose magnetic fields could be fitted adequately with a two-dipole model (five out of nine), for four subjects no model could be fitted due to too large noise in the data.

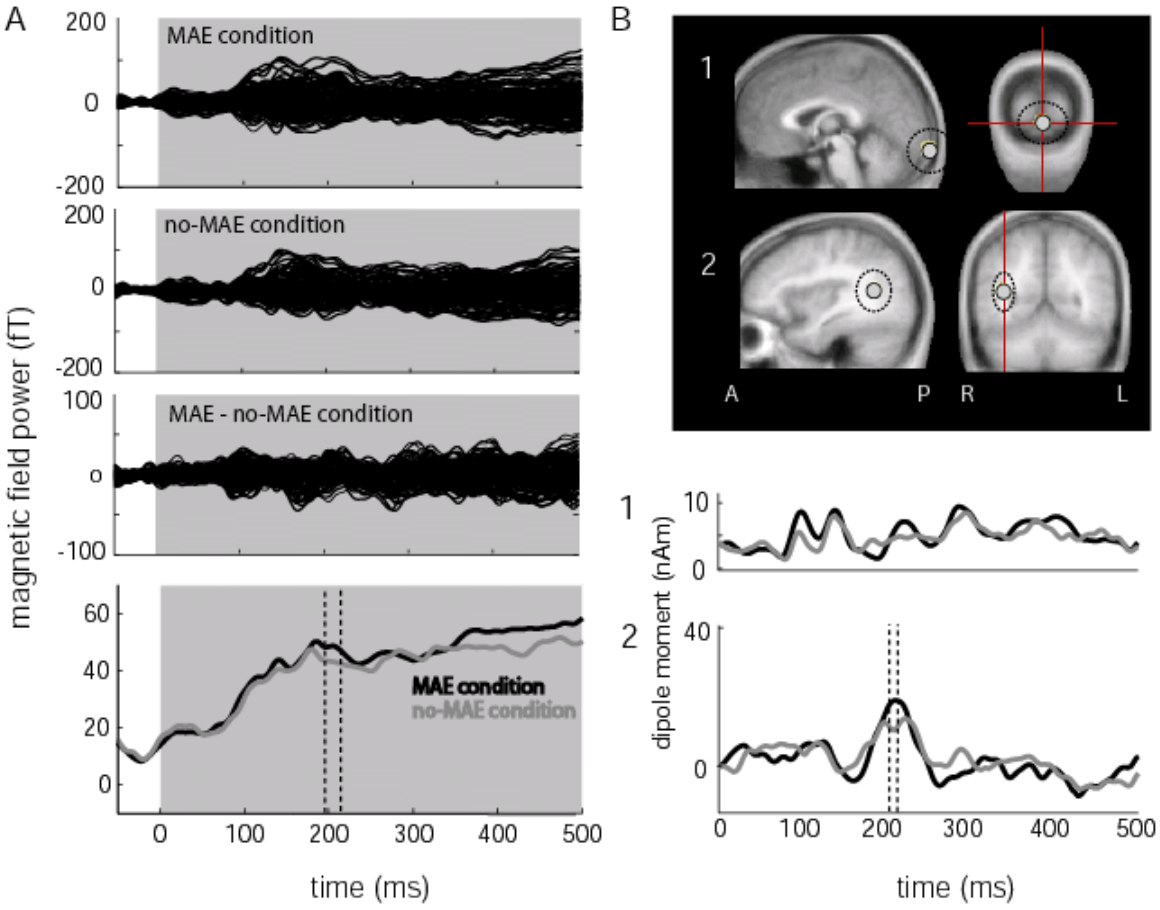

Figure 5) Neuromagnetic responses obtained under the MAE and no-MAE condition; group data (experiment 2). A, Upper three panels: group averages of evoked neuromagnetic responses (9 subjects, 149 sensors overlain) shown as a function of time for two conditions and their difference; MAE test phase (500 ms) is marked in grey. The fourth panel shows the mean global field power signals, i.e. the root mean squared neuromagetic responses across all channels, averaged over all subjects for the MAE (black) and no-MAE condition (grey). The time period in which the difference between the two conditions surpassed the noise level measured during the 50ms pre-stimulus period by at least 3STD is marked with broken lines (196 – 212 ms after stimulus onset). B, Dipole locations (open circles) modelling the magnetic field across the period of interest (first 250 ms of the RDP presentation) calculated from the data averaged over the two conditions for each subject separately (L: left; R: right; A: anterior; P: posterior). The broken circles mark the STD of the localisation between the 5 subjects used for the dipole analysis. The upper lineplot depicts dipole moments over time for dipole 1 (upper picture) averaged over subjects. Grey lines depict dipole moments over time obtained from trials of the no-MAE condition and black lines from the MAE condition. Dipole 2, depicted in the lower lineplot (with identical convention) shows for the time period between 200- 212ms a difference between conditions which surpassed the noise level measured during the 50ms pre-stimulus period by at least 3STD as indicated with two black dotted lines.

Results of experiment 2 were also in good agreement with those obtained from experiment 1 regarding the GBA responses, which similar to the dipole patterns described before were characterized by a change in side. The significant increase in GBA activity on the group level for the MAE condition was now confined to the right lateral parietal cortex ($p < 0.05$ corrected, Fig. 6A) in a similar frequency range (Fig. 6B, 75 – 76 Hz). A significant correlation ($r = -0.880$, $p < 0.05$ corrected, frequency band 95 – 96 Hz) with the size of the MAE was now found for a sensor lying above the left hemisphere (Fig. 6C). Although these two effects were not observed for clusters of sensors such as in experiment 1, the location of sensors showing the statistically significant effects were almost identical for the two

experiments. Specifically, the aforementioned increase in GBA during viewing of the MAE was associated with the right-sided sensor RP33, mirroring the left-sided LP33 – the caudal neighbour of the left LP23 - where the GBA increase had been revealed in experiment 1. The significant correlation of the GBA with the perceptual MAE, as depicted in Fig. 6F, was observed for the left posterior sensor (LT44) located a bit more rostral with respect to its contralateral analogue (RO41) that had shown a significant correlation with the MAE in experiment 1. Also, the frequency range of this effect was very similar (Fig. 6D, 95-96 Hz) compared to experiment 1. Again, we analyzed the time course of the MAE-associated effects by calculating the probability of the MAE associated difference in GBA for the parietal sensor and the probability of the correlation between the perceptual MAE and the spectral power for the ipsilateral sensor. As shown in Fig. 6E, the probability of the statistical measures for both sensors reached their maximum around 200 ms after the onset of the MEG-stimulus, without, however, deviating from baseline before stimulus onset.

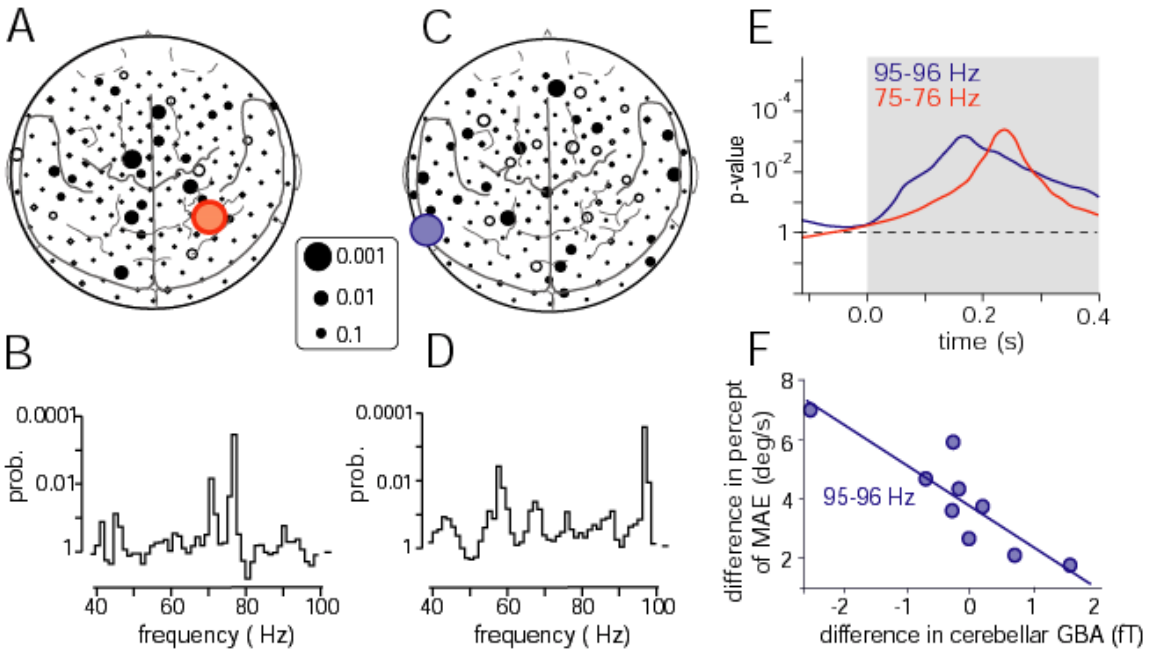

Figure 6) MEG correlates of the MAE (experiment 2; same conventions as in Fig. 3). ***A,*** Probabilities of spectral amplitude differences in GBA (70 ± 2.5 Hz) observed for the group of subjects between the MAE condition and the no-MAE condition during observation of the motion noise stimulus. The red colored circle marks a parietal sensor (RP33) which shows a significant increase in GBA in the MAE condition ($p<0.05$, corrected for multiple comparison) ***B,*** Frequency distribution of the p-values depicting the level of statistical significance of the difference of MEG activity between the MAE and no-MAE condition recorded from sensor RP33 (marked in red color in A) ***C,*** Probabilities of the correlation between the MAE and GBA mapped across all sensors of the MEG sensor array. Filled circles mark those sensors which show a negative correlation between the individual change in spectral GBA amplitude (94 ± 2.5 Hz) and the individual change in MAE. The blue circle marks a sensor (LT44) with a significant correlation ($p<0.05$, corrected for multiple comparison). ***D,*** Frequency distribution of the p-values depicting the level of statistical significance of the correlation between GBA recorded from sensor LT44 (marked in blue color in B) and the MAE. ***E,*** Time courses of GBA effects for the sensors that showed significant effects. ***F,*** The individual difference in the size of the GBA in the range of 94± 2.5 Hz recorded from sensor LT44 for the MAE condition as compared to the non-MAE condition shows a significant correlation with the individual difference in the size of the MAE for the two conditions (9 subjects).

We did not find a significant correlation between the individual differences in spectral power of the GBA picked up by the posterior inferior sensor (experiment 1: RO41, experiment 2: LT44) and the quality of fixation as assessed by the difference in mean retinal image velocity in the two conditions, neither for experiment 1 nor for experiment 2.
Finally, we add that we tried to delineate the underlying sources of the two MAE related gamma band responses by means of synthetic aperture magnetometry (SAM; Robinson and Vrba, 1999). Comparing the GBA elicited by the two conditions for all subjects by considering only the relevant frequency band and all sensors during 200 – 400 ms after test phase onset we failed to produce a consistent localization. This, however, may not be surprising in view of the tininess of the signals at stake.

Discussion

We used magnetoencephalography (MEG) in order to track down the neuronal circuits underlying the generation of the motion after effect (MAE), the illusion of visual motion associated with a stationary scene, induced by prolonged exposure to a preceding motion stimulus (Purkinje, 1825; Wohlgemuth, 1911). We observed an electrophysiological signature of the MAE in the form of increased global field power. The magnetic field distribution associated with the paradigm could be explained reasonably well by assuming two equivalent current dipole sources, a midline source in primary visual cortex, and a second, bilateral source in parietooccipital cortex close to the location of human area MT+. Only the latter exhibited a significant difference between the MAE and the no-MAE condition, whereas the moment of the V1 dipole did not show a change in its strength between the two conditions. Whereas many studies showed a change in the well known motion induced evoked potentials (motion onset responses), namely an increase in the positive P1 over the occipitotemporal area and a reduction of the negative N200 after motion adaptation (for overview see Mather et al., 1998) there are few electrophysiological studies which actually explore the time during the illusory motion perception. Some groups reported an amplitude increase in the negative N200 component as answer to motion offset after long adaptation (motion presentation) compared to short adaptation (Niedeggen et al., 1992) whereas others reported a decrease in the N200 amplitude in the maximally compared to the minimally adapted condition (Hoffmann, et al., 1999). Also a positive component has been reported to exclusively change due to adaptation namely to increase in amplitude 160 ms after test stimulus onset (Kobayashi et al., 2002). The only previous electrophysiological investigation offering a more or less exact cortical basis of the MAE in humans has been contributed by Uusitalo and colleagues (1997). In this study, subjects were exposed to a rotating or stationary central stimulus respectively for one second, succeeded by a blank period of 2 s duration in which only a fixation spot was visible. In 4 of the 7 subjects, sustained magnetic activity, on average arising 200-500ms after offset of the adapting stimulus, was significantly smaller if instead of the rotating stimulus a stationary stimulus had been presented. Resorting to a multi-dipole model the authors could localize a dipole between the occipital and temporal lobe, partly explaining this difference in sustained activity (80 – 800 ms) in 1 subject (Uusitalo et al., 1997). A major limitation of this study was the lack of a direct measurement of motion perception due to adaptation on a trial to trial basis. Largely qualitative information on the absence or presence of a MAE was based on verbal reports, subjects provided after the

experiment. A second, quite resent study investigating the velocity after-effect reported decreased response amplitudes to motion stimuli in the direction of a previously shown adaptation stimulus compared to the response to motion stimuli in the direction opposite to the adapted one. This change in response was observed 200 -300 ms after teast stimulus onset and was located mainly in the temporooccipital area (Amano et al., 2005).

Our consistent demonstration of a later, parietooccipital dipole specifically related to the occurrence of a MAE, quantitatively demonstrated with state-of-the art psychophysical techniques supports and extends these earlier observations, suggesting a role of area MT+ in the generation of a MAE. The fact that the latency as well as the localization of the parietooccipital dipole deviated slightly in our second study, in which the visual stimuli had been moved to the other side, is most probably a consequence of the much higher noise level in this experiment compared to experiment 1. These two MEG studies, the one by Uusitalo and the one at hand, suggesting differential roles of early and later parts of visual cortex in the generation of the MAE, are fully compatible with the results obtained by recent TMS and fMRI studies. As described in the introduction, both approaches have singled out the MT+ complex as connected to the MAE in man. On the other hand, fMRI failed to reveal specific BOLD responses associated with the occurrence of a MAE in primary visual cortex (Tootell et al., 1995; He et al., 1998; Culham et al., 1999; Taylor et al., 2000; Hautzel et al., 2001).

The second electrophysiological signature of the MAE in this study was oscillatory activity in the gamma-band range. In our study induced gamma band activity (GBA) reflecting the MAE was observed in channels over two locations. In general a significant change in GBA observed in a single sensor only might at first sight seem implausible since one source evokes a dipole structured magnetic pattern. However single sensors are often observed to be significant (Kaiser et al., 2000; 2004a; Lutzenberger et al., 2002) and Kaiser and colleagues offer a nice explanation. They argue that a singular GBA can be explained by assuming a more complicated underlying source structure and executing simulations they could show that quadrupoles and even more octopoles or circular currents yield a strong maximum between the sources but considerably weaker minima on the outside. It is very likely that only these maxima reach statistical significance. Importantly this model would also imply that the sources are located close to the area below the sensor with the highest GBA (Kaiser et al., 2000).

The first sensor that showed a relation between GBA and MAE one was found over parietooccipital cortex contralateral to the side of the visual field stimulated, a location which is in principle compatible with a source in dorsal extrastriate cortex, although all efforts failed to accurately localize the source. GBA was observed during the period of time in which an incoherent random dot pattern (RDP) was present but perceived as moving due to preceding adaptation. Importantly, the strength of gamma oscillations in the parietooccipital location, most probably reflecting processing in underlying cortex was not related to the size of the MAE measured in the individual subject.

In order to come up with an interpretation of the emergence of parietooccipital gamma oscillations during the emergence of a MAE, but not quantitatively related to its size, it is pertinent to consider previous observations and thoughts on the possible neuronal basis of the MAE. It has been suggested by Mather and colleagues (Mather et al., 1998) that exposure to a strong motion stimulus not only leads to a decrease in the activity of neurons with a preferred

direction matching the direction of the adapting stimulus but also to an increase in the complementary pool of neurons, sharing a preferred direction opposite to the adapted one. This latter increase is thought to be a consequence of reduced inhibition from the former pool of neurons and both changes, the decrease of firing in the adapted pool and the increased firing in the complementary pool are thought to take part in the formation of the MAE (see Mather and Harris, 1998). The fact that neurons in monkey area MT indeed show a reduced responsiveness after adaptation in the preferred direction, however, an enhancement after adaptation in the null direction, is in full support of this view (Kohn and Movshon, 2003; Petersen et al., 1985). Hence, the formation of a MAE is accompanied by an increase in the firing of a group of neurons sharing a certain preferred direction, similar to the increase in firing resulting from an increase in motion coherence in standard random dot pattern (Britten et al., 1992; Newsome et al., 1989; Britten et al., 1996). Interestingly, in humans GBA has been found to correlate positively with increasing motion coherence in RDPs (Siegel et al., 2006) at a very similar sensor distribution as our parietooccipital gamma focus. Hence, increasing motion coherence enhances the spiking rates of MT neurons and in humans, increasing motion coherence is associated with increases in GBA. The tentative conclusion to be drawn from these observations then might be that any condition leading to the selective activation of neurons sharing the same trigger feature will lead to increases in spiking activity as well as the formation of GBA, of course suggesting a common mechanistic basis of the two. Actually, synchronous oscillations, most likely underlying the extracortical electromagnetic field oscillations detected by MEG, are known to occur more frequently between neurons sharing the same preferences. For instance, V1 neurons with similar preferred stimulus features show synchronous firing in the gamma range when activated jointly by a preferred stimulus in cat (Eckhorn et al., 1988; Gray et al., 1989; Freiwald et al., 1995) and monkey (Ts'o et al., 1986; Livingstone, 1996). In monkeys, it could, moreover, be shown that the neuronal coherence is the higher the more similar the orientation preferences of neurons are (Frien et. all, 2000). Similar findings have been observed in monkey area MT (Kreiter et al., 1996). Actually, the odd one out is motion coherence, whose study has as yet yielded conflicting results as one group found gamma oscillation in area MT to correlate with motion coherence (Nase et al., 2003) whereas another one failed (Bair et al., 2001).

As pointed out in the introduction, the emergence of GBA has been interpreted as a possible correlate of increased binding between features leading to a coherent percept. However, in studies of coherent motion perception, it is clear that the emergence of GBA does not coincide with the threshold of the perception of global motion (Siegel et al., 2007). Rather, GBA increases monotonically with the amount of coherence in the stimulus and, actually, there is a stronger increase in GBA between 50% coherence and 100% compared to 12.5% and 25% even though the detection threshold is at about 14%. By the same token, also the parietooccipital GBA in the study at hand, occurring during the perception of an MAE, did not correlate with the strength of the MAE. Hence, at least parietooccipital GBA, while preferring conditions that may lead to specific global percepts, can hardly be their mechanistic basis. Rather, parietooccipital GBA seems to reflect the extent of selective activation of a set of neurons, sharing the same trigger features.

Unlike the parietooccipital GBA, the second, posterior GBA focus, did show a correlation with the percept and was increased in subjects exhibiting a higher MAE compared to those

showing a lower one. That this GBA was indeed correlated with the MAE and was not related to coarse eyemovements is important to note even though we can not exclude involvement of microsaccades due to the low temporal resolution of our eyetracker (50Hz). Unfortunately, it was not possible to conclusively locate the point of origin of this activity. Two sources seem conceivable, namely primary visual cortex and the cerebellum. Since dealing with strong visual stimuli the first explanation might seem more intuitive. However, several considerations militate against the interpretation that GBA in this posterior location, correlating with the strength of the perceived MAE, originates from early visual cortex. 1. TMS of human MT+ was reported to disrupt the perception of the MAE, while TMS of V1 did not (Theoret et al., 2002). 2. By the same token, the fMRI studies discussed in detail earlier failed to demonstrate MAE-associated BOLD-activations in V1 (Culham et al., 1999; Taylor et al. 2000; Hautzel et al., 2001). 3. The percept related GBA was not observed contralateral to the hemifield stimulated but ipsilateral to it, obviously at odds with the crossed nature of the visual system.

An area we might expect to exhibit an ipsilateral activation because of its crossed connection with the cerebrum is the cerebellum. That the detection of activity coming from the cerebellum is by no means impossible for MEG has been shown repeatedly since neuromagnetic activity could be located by means of ECD models (Tesche and Karhu, 2000) as well as by applying beamforming techniques (Timmerman et al., 2003; Gross et al., 2002). If the posterior GBA observed in our experiment indeed originated from the cerebellum, a concern, close at hand would of course be that it reflected the hand movement required by the paradigm rather than the MAE. However, this concern can be dispelled clearly as the topographically circumscribed posterior GBA was found ipsilateral to the moving hand movement in experiment 1 but contralateral to it in experiment 2. The idea of a cerebellar involvement in the MAE is actually less odd as it may appear at first sight as also a recent PET-study by Hautzel et al. (2001) has implicated the cerebellum in this perceptual illusion. These authors reported changes in the metabolic signal following motion adaptation not only in MT+ but also within the cerebellar cortex. However, Hautzel and colleagues argue that it was not specifically the MAE which was represented in the cerebellar activity since in a further reference condition with identical attentional demand but no perception of a MAE an elevated cerebellar BOLD signal was found as well.

A role of the cerebellum in the processing of visual motion, possibly suggested by our experiment would in principle be in accordance with the finding of quite specific deficits of visual motion perception in patients suffering from cerebellar disease (Ivry and Diener, 1991; Nawrot and Rizzo, 1995, 1998; Thier et al., 1999). This prompts the interesting question, if patients suffering from cerebellar disease might also manifest an altered MAE. Obviously, this would have to be expected if the visual motion perception deficit exhibited by patients and a MAE associated cerebellar GBA both reflected a common specific role of the cerebellum in visual motion processing.

Literature

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2.7 Altered motion aftereffect in cerebellar patients

Introduction

Deficient motion perception has been reported in patients with cerebellar lesions by various independent groups (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier et al., 1999; Jockisch et al., 2005). This perceptual impairment manifests itself in such a way that in a random dot display more dots have to move coherently in one direction in order to enable patients to detect the prevalent global motion direction. The strength of motion coherence is depicted in area MT as shown by an increased firing rate of MT neurons with rising motion coherence (Britten et al., 1992; Newsome et al., 1989; Britten et al., 1996). The same relationship was found for human area MT+ (a complex of various extrastriate areas including area MT) using imaging techniques (fMRI: Rees et al., 2000; Braddick et al., 2001; MEG: Aspell et al., 2005: Maruyama et al., 2002; Händel et al., 2007). Interestingly, this motion coherence dependent modulation in extrastriate areas including area MT+ was reported to be decreased in cerebellar patients and its reduction to be correlated with the perceptual impairment of coherent motion direction (Händel et al., in preparation).

Area MT and neighbouring cortex also seem to be the major substrate of the perception of illusionary motion induced by motion adaptation. This is indicated by single-unit recordings from the visual cortex of monkeys (Petersen et al., 1985; Kohn et al., 2003) and fMRI (Tootell et al., 1995; He et al., 1998; Culham et al., 1999; Taylor et al., 2000), PET (Hautzel et al., 2001) and TMS (Theoret et al., 2002) studies of the human brain investigating the motion after effect (MAE), a visual motion illusion emerging after prolonged exposure to coherent visual motion (Wohlgemuth, 1911). If area MT+ codes for real and illusionray motion in a similar way altered MT+ activity in patients with cerebellar lesions might not only lead to a deficit in perception of real motion but also to altered perception of illusionary motion. First hints that the cerebellum is linked to the processing of illusionary motion are reported by Tikhonov and colleagues (2007) describing a correlation between the strength of the MAE and fast gamma band oscillations possibly originating from the cerebellum.

However, instead of a common role of the cerebellum in the perception of real and illusionary motion, also other ways of influence seem possible: Self-generated movements alter the sensory input by stimulating peripheral afferents and sensor organs and the resulting signal is called the reafferent part of the total sensory input. In order to differentiate this reafference from sensory input due to environmental changes it is essential to identify and finally perceptually ignore the reafference. The concept named *Reafferenzprinzip* postulates that this might be achieved by subtracting a negative copy of the descending motor command (called efference copy or corollary discharge) from the total sensory input (von Helmholtz, 1867; von Holst and Mittelstedt, 1950; Sperry, 1950). The recently suggested term reference signal shifts the focus away from the concept of a simple copy of a motor command towards a highly adjustable signal reflecting not the motor command itself but rather the predicted sensory consequences of it (Haarmeier et al., 2001). Haarmeier et al. (2001) showed that the prediction of the visual consequences of smooth-pursuit eye movements could be modulated by adapting background stimuli in such a way that the mismatch between expected and perceived retinal motion was reduced. This resulted in an altered motion perception under

smooth pursuit. A follow up study by Lindner et al. (2006) further reported that the size of this perceptual alteration correlated negatively with cerebellar BOLD signals.
There are several other studies indicating an involvement of the cerebellum in the processing of such sensory predictions. Studying weakly electric fish Bell (1981) showed that the cerebellar-like structure of these animals sets off a prediction of the expected sensory consequences of self-produced electrical fields against the actual electrical field measured. Similarly, Blakemore and colleagues suggest the cerebellum to contribute to our ability to distinguish between external and self-produced tactile stimulation based on the observation that cerebellar BOLD responses were altered if a certain movement would lead to a sensory consequence and therefore also to its prediction (Blakemore et al., 1998; 2001).
If also the MAE is affected by an altered prediction of the sensory consequences of eye movements, an interesting question will be if the modification of the cerebellum leads to an altered MAE independently of the deficit in perceiving real motion. The present study investigated this notion by examining a group of patients with cerebellar lesions on their ability to perceive and adapt to visual motion compared to healthy controls. Using a rather classical motion aftereffect paradigm it could be shown that motion adaptation indeed was altered in cerebellar patients but did not correlate with fixation difficulties or patients' ability to perceive real motion.

Materials and Methods

Subjects: Twelve patients (6 females, mean age 48 +/- 13 years, range: 29 - 70) and Sixteen age matched healthy controls (6 females, mean age 46 +/-12 years, range 29-69) participated in this study. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the guidelines of the local ethics committee of the medical faculty of the University of Tübingen, which approved the study. All of the subjects had normal or corrected to normal vision, controls had no history of neurological disease. The patient group varied from patients with focal lesions to those with degenerative diseases (see Table 1).

cerebellar disease	SCA6	SCA6	SCA6	IDCA	IDCA	IDCA	IDCA	IDCA	IDCA	IDCA	EA 2	PICA
age	60	70	65	58	47	51	34	29	44	38	46	34
sex	m	w	w	m	w	m	w	w	m	m	w	m
"MAE" > 2.5 STD	yes	no	yes	no	no	no	no	no	no	yes	no	no
"no-MAE" > 2.5 STD	no	yes	no	no	no	no	no	no	no	no	no	no
MAE diff. > 2.5 STD	yes	yes	yes	no	no	no	no	no	no	yes	yes	no
any eye parameter > 2.5 STD	no	no	no	no	no	no	no	no	no	yes	no	no
motion perception > 2.5 STD	no	no	no	no	-	-	yes	-	no	no	no	-

Table 1) Results with respect to patients' details: Diagnosis, age and sex. "Yes" and "no" indicates if any deviation from normal (2.5 STDs away from mean of control group) is found in their velocity judgment concerning the "MAE", the "no-MAE" condition and the difference between condition. Additionally it is indicated if eye movement parameters and the perceptual threshold of real, coherence modulated motion deviated more than 2.5 STDs from normal.

Three patients had a spinocerebellar ataxia type 6 (SCA6) and 7 patients were diagnosed with idiopathic cerebellar ataxia (IDCA). SCA6 and IDCA are thought to constitute forms of "pure cerebellar ataxia" (Manto and Pandolfo, 2002). One patient suffered from episodic ataxia type

2 (EA 2), a neurological disorder which is also confined to the cerebellum and one other patient had purely cerebellar lesions caused by a left sided posterior inferior cerebellar artery (PICA) insult 2 years before the experiment. Detailed information about results with respect to the type of cerebellar deficit can be seen in Table 1.

Stimuli: Stimuli were rear projected onto a large translucent screen (CRT projector, frame rate 60 Hz, 800 x 600 pixel) positioned at a viewing distance of 142 cm. Viewing was binocular. A red spot (diameter 10 min of arc), presented in the middle of the screen, served as a gaze fixation target during the whole trial. The visual motion stimuli were projected unilaterally into the right visual hemifield centered at an eccentricity of 12.5 deg on the horizontal meridian. Stimuli subtended a visual angle of 9 x 9 deg and consisted of 300 white dots (diameter: 15 min arc; luminance: 65 cd/m2; individual life-time: 200 ms) which were randomly plotted on a dark background. Dots that left the stimulus aperture were re-plotted in randomly chosen positions within the aperture. Each experimental trial (see Fig. 1) began with a blank interval (duration 0.5 s), in which only the central fixation spot was visible. This interval was followed by a priming phase lasting 5.0 seconds during which a random dot pattern (RDP) was presented (Fig. 1). Different for two conditions applied, the 300 dot elements would either move coherently downward ("MAE" condition) or would move incoherently i.e. in individually varying directions (motion-balanced) drawn from a distribution of directions spanning 360 degrees ("no-MAE" condition).

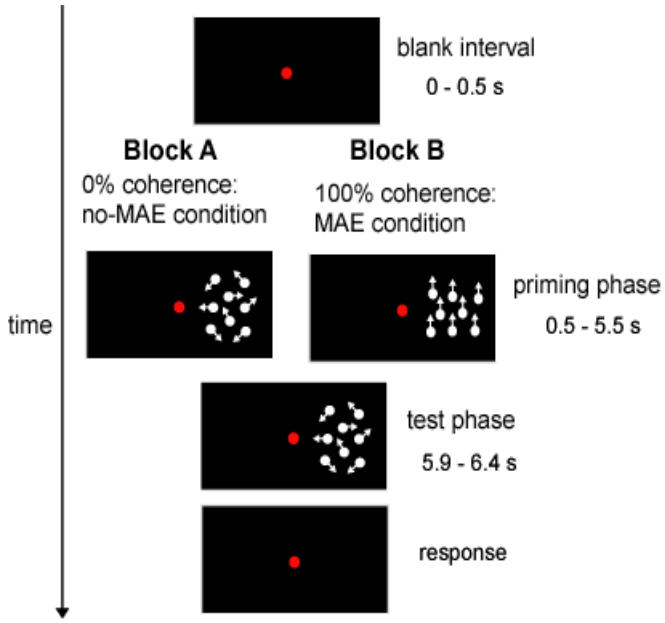

Figure 1) Time course of the stimulus. The stimulus consisted of 4 periods. Each trial began with a blank interval (duration 0.5 s), in which only the central fixation spot was visible. This interval was followed by a priming phase lasting 5.0 seconds during which a 9 x 9 deg random dot pattern (RDP, 12.5 deg centered to the left, consisting of 300 white dots) was presented. In the "no-MAE" condition these dots moved incoherently, in the "MAE" condition they moved coherently downward. After a subsequent second blank interval (0.4 s) a test phase (duration: 0.5 s) started where the dots moved more or less coherently up or down biased by a constant amount of vertical motion added vectorially to all dot elements (see methods). The size and direction of the added vector was varied by means of an adaptive staircase procedure. At the end of each trial, subjects were required to indicate their perceived motion direction during the test phase by pressing a button.

After a subsequent second blank interval (0.4 s) the test phase (duration: 0.5 s) started. In this test phase, again a RDP was presented in which the dots moved in individually varying directions as described for the priming phase of the "no-MAE" condition, however, the RDP was now biased by introducing a constant amount of vertical motion added vectorially to all dot elements. The movement of each individual dot was given by summing the vertical bias vector, which was the same for all dots, and the individual dot velocity vector underlying the unbiased motion-balanced RDP. If the size of the biased motion vector corresponded to the

size of the oppositely directed MAE, the physical motion and the illusory motion annihilated each other, rendering the biased motion-balanced RDP perceptually stationary. At the end of each trial, subjects were required to indicate their perceived direction of global motion of the second RDP by pressing a button.

MAE: In order to determine the size of the vertical (downward) motion bias needed to render the stimulus stationary (velocity of subjective stationarity), the size of the added velocity vector was varied from psychophysical trial to psychophysical trial by means of an adaptive staircase procedure. The velocity of subjective stationarity at which subjects will guess the direction of global motion as indicated by equal numbers of upward and downward decisions was determined by performing a probit analysis over the responses obtained for all tested velocities (McKee et al., 1985) with subsequent chi-square goodness-of-fit tests.

Trials with coherent and incoherent visual motion during the priming phase ("MAE" versus "no-MAE" condition) were presented in two subsequent blocks. The sequence of these two blocks was pseudo-randomized across subjects. The actual MAE was then calculated from the difference between the velocity of subjective stationarity acquired during the non-adaptive block and if adaptation was induced. This made sure that any possible bias in answers would not influence the quantification of the MAE (see Tikhonov et al., 2007).

Motion perception: Additionally, the ability to perceive motion direction was tested in 8 out of 12 patients and 11 controls by using a similar paradigm as used by groups previously showing a motion perception deficit in cerebellar patients (Ivry and Diener, 1991; Nawrot and Rizzo, 1995; 1998; Thier et al., 1999; Jockisch et al., 2005). The visual stimulus consisted of a RDP which covered a square of 9 x 9 deg and was centered 12.5 deg right of the fixation point. The RDP, lasting 500 ms, consisted of 300 randomly plotted white squares (side length = 8 arcmin, lifetime = 200 ms,) which could move in all possible directions, at a common speed of 4deg/s. The amount of dot elements moving coherently in the same direction (left or right) was varied according to an adaptive staircase procedure. Subjects were instructed to keep fixation as accurately as possible during the whole trial and to indicate by a button press whether the perceived global motion direction was to the left or to the right. In order to assess the ability to discriminate the motion direction embedded in noise, the percentage of correct responses in the individual measurement was plotted as function of motion coherence and fitted by a probit function. The perceptual threshold was defined by the coherence level for which the probit function predicted 75% correct responses.

Eye movements: During all experiments, eye movements were monitored using a homemade video system taking the pupil's center as measure of eye position. Recordings were stored at a sampling rate of 50 Hz and analyzed offline in order to assess the quality of fixation. In particular, the following oculomotor parameters were analyzed, i.e. deviations from the fixation point (eye position) and the number, velocity and amplitude of saccades. To this end, the means of the different oculomotor measures were calculated for the "no-MAE" and "MAE" condition during the priming phase (1500 -6500 ms) and the test phase (6900 – 7300 ms) separately in each subject. Dependencies of eye movements on the perceived MAE were tested using a linear regression analysis. Patients suffering from nystagmus were identified by visual inspection of the single trials in which these rapid involuntary rhythmic eye movement, with their characteristic shape (eyes moving quickly in one direction and then slowly in the other) are easily identified. For one subjects no data was available for the "MAE" condition

and for one subject “no-MAE” data was missing due to technical problems during the experiment. All analysis was calculated using MATLAB (version 6.5.1).

Results

For the 12 patients participating in our study the mean velocities which had been judged to be stationary after exposure to the priming stimulus in the “MAE”-condition amounted to -4.9 +/- 3.7°/s, which corresponds to the perception of upward motion. The mean measured velocities in the absence of a priming stimulus in the “no-MAE” condition amounted to 0.3 +/- 1.6°/s. This velocity bias measured in the absence of induced motion is likely to reflect a response bias for upward motion. Hence, it is the difference between conditions (judged velocity) that reflects the true size of the MAE. The mean value acquired for the patient group was -5.2 +/- 4.3°/s. For the measured control group (age and sex matched) the velocity judgment measured during the “MAE” condition was -4.7 +/- 1.5°/sec whereas during the “no-MAE” condition it amounted to -0.8 +/- 1.2 °/sec. The MAE calculated via the difference between conditions was -3.8 +/- 1.3°/s.

Since a change in adaptation might result either in an increased or a decreased MAE the data was analyzed by means of a threshold, marking the range of a normal MAE choosing the mean of the normal controls +/- 2.5 standard deviations (STD). While for the “no-MAE” condition only one patient lay outside this range (Fig. 2A) 3 patients were above the 2.5 STD threshold in the “MAE” condition (Fig. 2B). However, when looking at the actual MAE (the difference between “MAE” and “no-MAE” condition) the number of patients that lay outside the normal range increased to 5 (Fig. 2C).

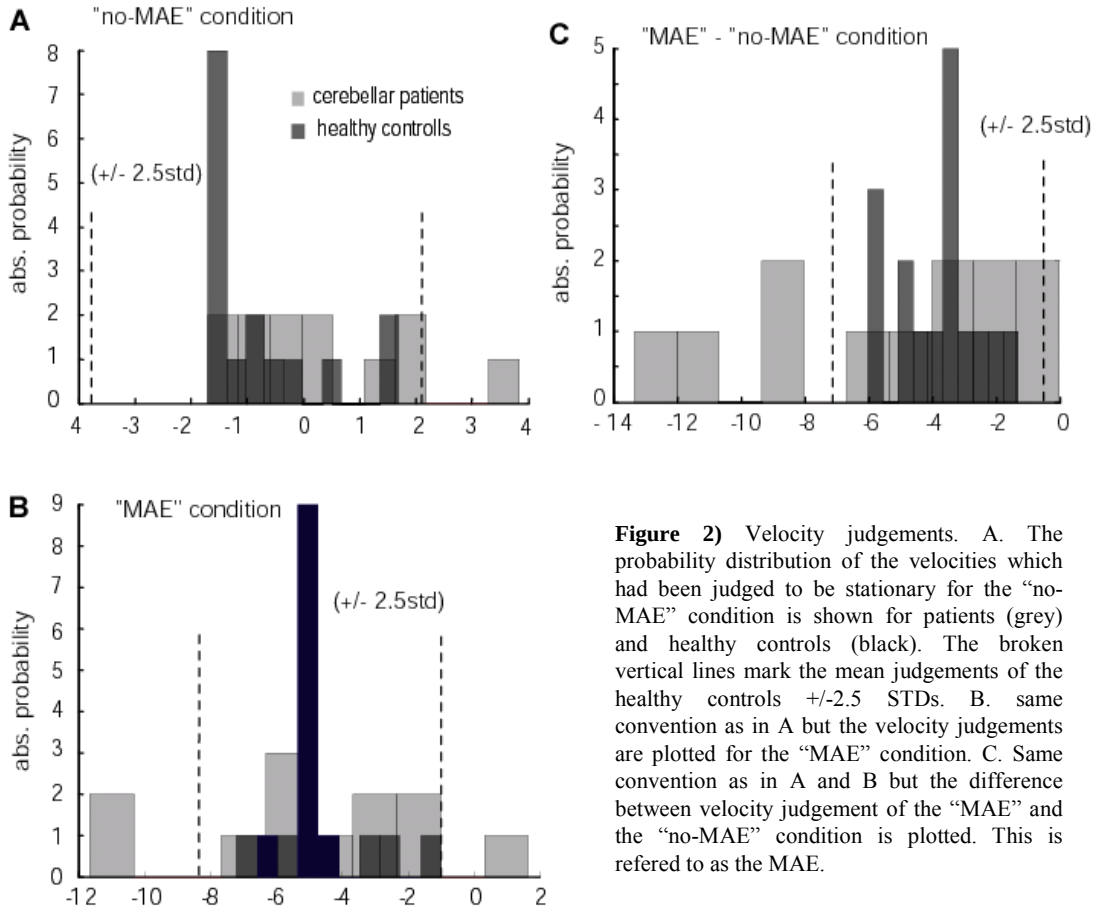

Figure 2) Velocity judgements. A. The probability distribution of the velocities which had been judged to be stationary for the “no-MAE” condition is shown for patients (grey) and healthy controls (black). The broken vertical lines mark the mean judgements of the healthy controls +/-2.5 STDs. B. same convention as in A but the velocity judgements are plotted for the “MAE” condition. C. Same convention as in A and B but the difference between velocity judgement of the “MAE” and the “no-MAE” condition is plotted. This is refered to as the MAE.

In order to secure that no eye movement deficits were the cause of possible differences between patients and controls various parameters of eye related movements were carefully analyzed. Fig. 3 and 4 show the perceptual velocity values (for the "MAE", the "no-MAE" condition and the difference between conditions) and the corresponding values of the analyzed eye movement parameters.

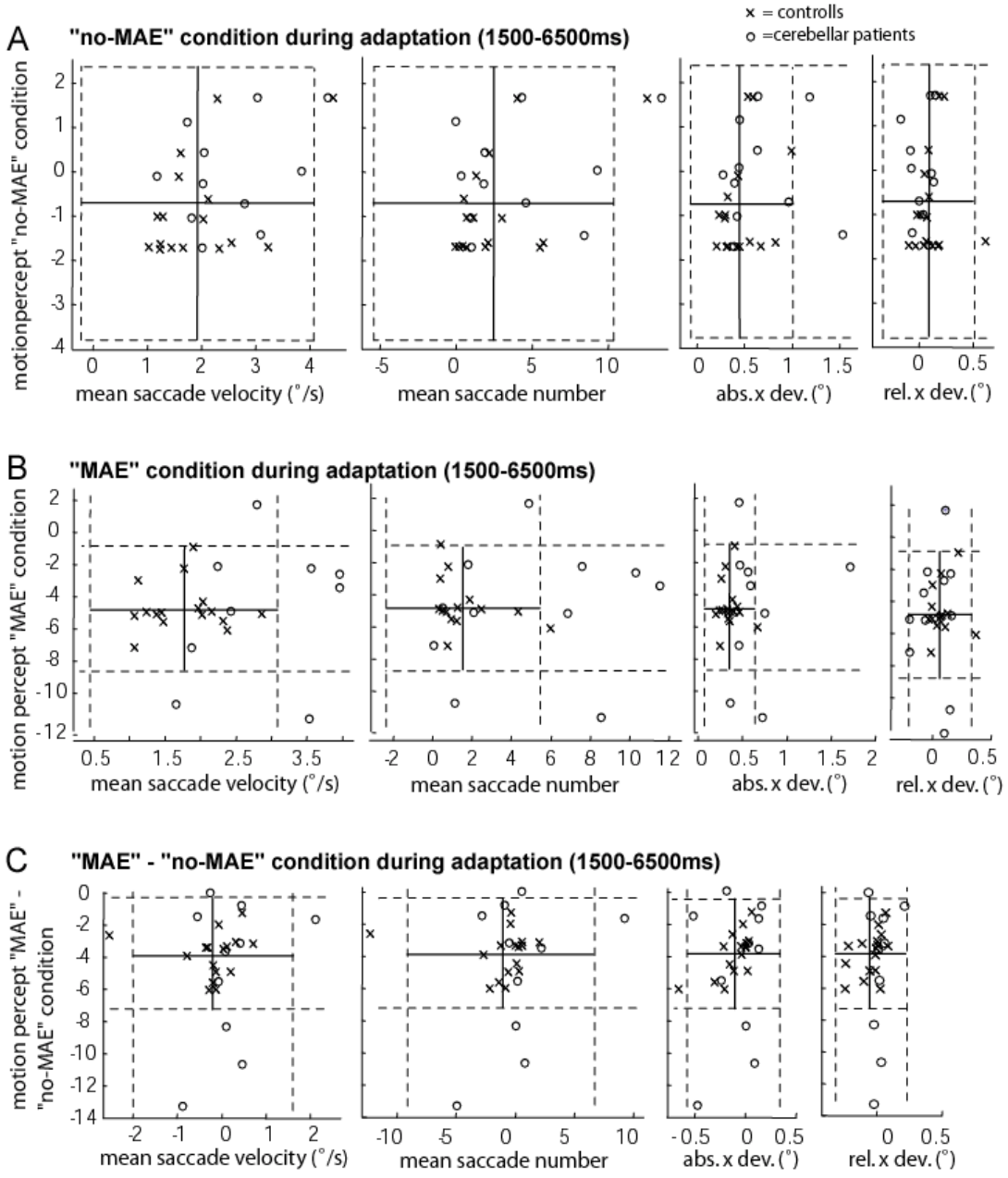

Figure 3) Eye movements during priming stimulus. The individual perceptual velocity values (y-axis) plotted against the corresponding values of the four eye movement parameters analysed (X-axis) plotted for the time during the priming stimulus (1500-6500 ms). Specifically, from left to right the velocity at which the test stimulus was judged as stationary is plotted against the velocity of the saccades executed during the adaptation period (left), the number of saccades (middle-left), the absolute horizontal deviation from the fixation spot (middle-right) and the relative horizontal deviation (right). Within each plot the broken lines mark the mean values of the healthy controls +/-2.5 STDs. Black stars mark the individual data points from the control group and grey circles from the cerebellar patient group. The perpetual velocity values plotted against the corresponding eye movement parameter values are shown for the "no-MAE" condition (A), the "MAE" condition (B) and the difference between the conditions (C).

time periods, i.e. the time during the priming stimulus (Fig. 3, 1500-6500 ms) and the time period where the test stimulus was presented (Fig. 4, 6900-7300 ms). Within each plot the broken lines mark the 2.5 STD thresholds which make it easy to observe if those patients who showed an altered MAE also showed diverging values concerning eye movements.

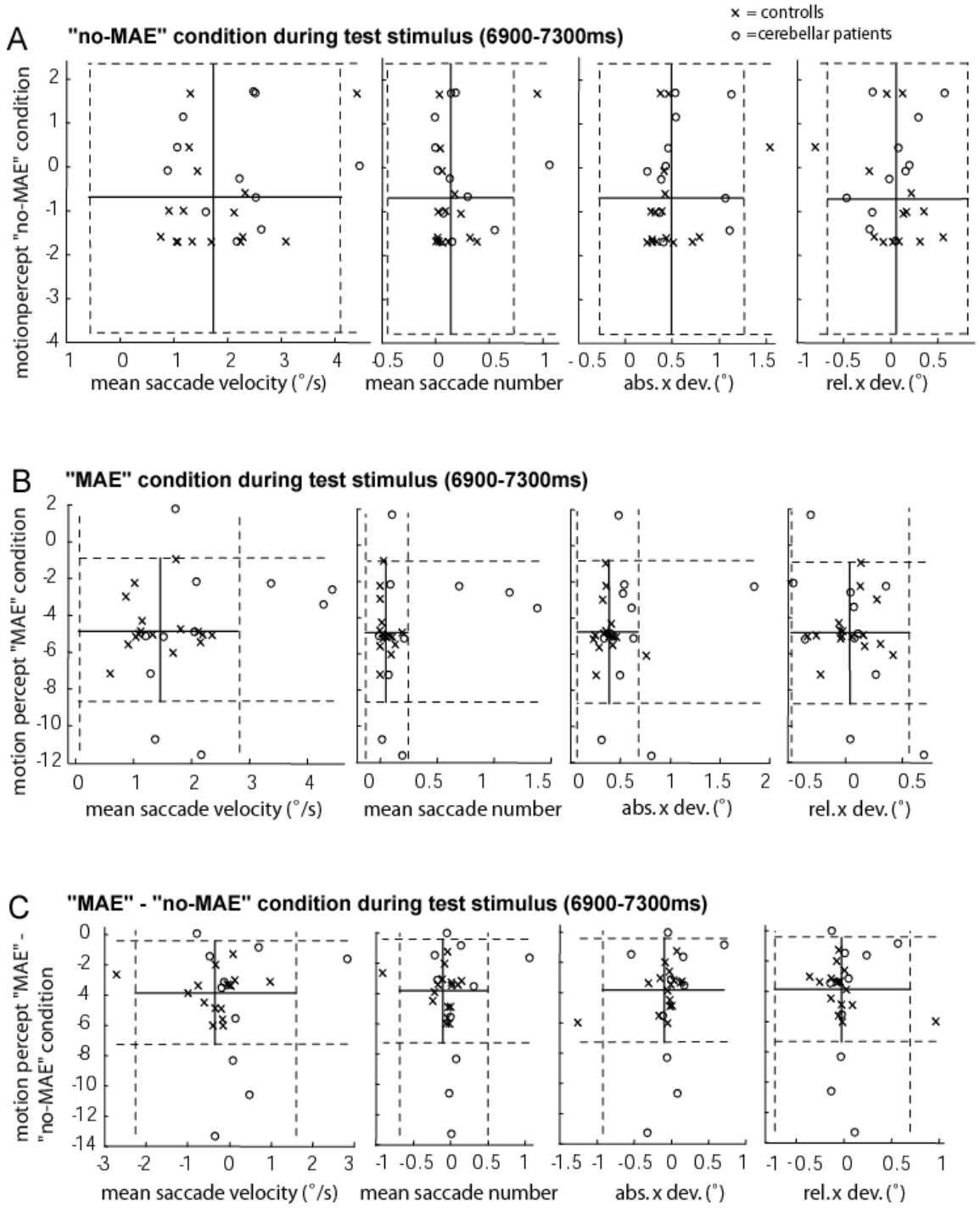

Figure 4) Eye movements during test stimulus. Conventions as in Fig. 3 but the plotted values are now collected during the test stimulus (6900-7300 ms). Velocity values of the stationary percept are plotted against the velocity of the saccades (left), the number of saccades (middle-left), the absolute horizontal deviation from the fixation spot (middle-right) and the relative horizontal deviation (right). Within each plot the broken lines mark the mean values of the healthy controls +/-2.5 STDs. Black stars mark the individual data points from the control group and grey circles from the cerebellar patient group. The perceptual velocity values plotted against the corresponding eye movement parameter values are shown for the "no-MAE" condition (A), the "MAE" condition (B) and the difference between the conditions (C).

There was only one patient who showed a changed velocity percept and at the same time enlarged eye movement parameters in the "MAE" condition. Specifically, this patient (suffering from IDCA; see Fig. 1B) showed a increased velocity of saccades, number of saccades and absolute horizontal deviation from the fixation spot during the priming stimulus (Fig. 3B) as well as an increase in the absolute and relative deviation from the fixation target during the test stimulus (Fig. 4B). A linear regression calculated for the patient group over the MAE values and the different eye movement parameters for both time periods separately showed no significant correlation ($p > 0.05$, uncorrected).

The ability to perceive real motion as plotted in Fig. 5 was defined by the percentage of dots which had to move coherently in one direction in order to correctly identify 75% of the trials presented. Mean motion detection threshold for the 11 control subjects measured with this paradigm was 31 +/- 16% STD, the 8 patients showed a mean motion perception threshold of 34 +/- 24% STD. The mean of the two groups were not significantly different (T-test p= 0.7). The one patient who showed a motion perception threshold 2.5 STD above the mean threshold of healthy controls did not exhibit an altered MAE (Fig. 5).

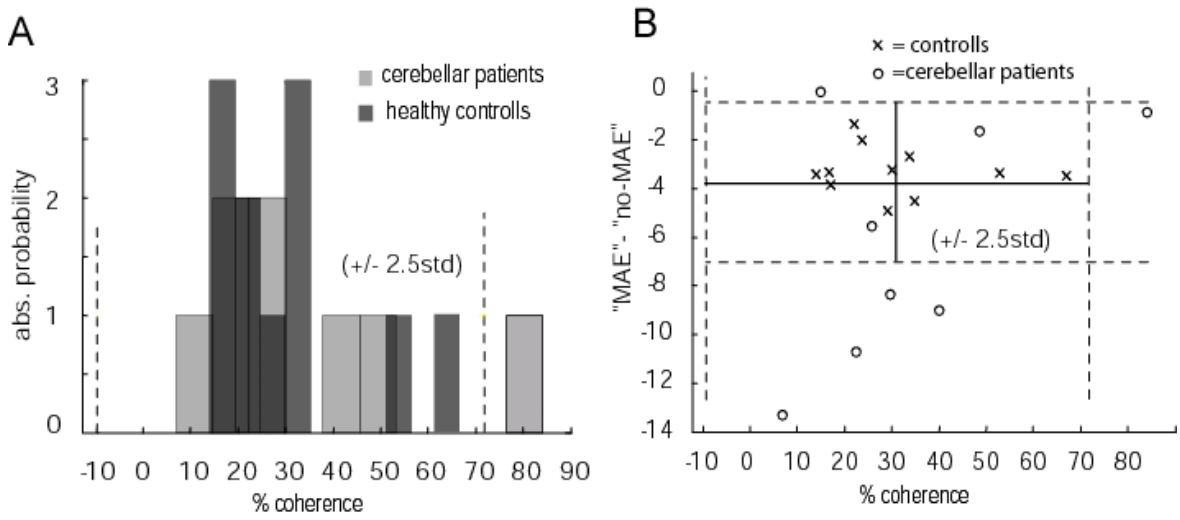

Figure 5) Motion perception. A. the probability distribution of the motion perception (defined as percentage of dots moving coherently in one direction in order to identify 75% correct) is shown for patients (grey) and healthy controls (black). Mean motion detection threshold for the11 control subjects (31 +/- 16 STD) and the 8 patients (34 +/- 24 STD) were not significantly different (T-test p= 0.7). B. The individual MAE values (y-axis) are plotted against the corresponding motion perception values (X-axis) for patients (blue) and controls (red). The broken lines mark the mean values of the healthy controls +/-2.5 STDs.

Discussion

The main finding of this study was, that patients suffering from cerebellar damage can show a significantly altered MAE compared to age matched controls. However, in order to draw the conclusion that the cerebellum is indeed involved in illusionary motion perception, some possible concerns have to be met first.

As described in the methods patients were picked carefully in order to include only subjects with a purely cerebellar deficit but no additional cortical or subcortical dysfunctions. It should be further noticed that 4 out of 5 patients showing an altered MAE were fallen ill with either a genetically confirmed spinocerebellar ataxia type 6 (SCA6, 3 patients) or with an episodic ataxia type 2 (EA 2, 1 patient). SCA is a hereditary neurodegenerative disorder (autosomal

dominant) where type 6 has been described as “pure” cerebellar ataxia with atrophy limited to the cerebellum (Schöls et al., 2004). EA 2 is a rare neurological disorder also of autosomal dominant inheritance resulting from dysfunction of a voltage-gated calcium channel by mutations of a calcium channel gene, encoding a certain subunit of this calcium channel which is primarily expressed in Purkinje cells. A slow progression of cerebellar signs accompanied by a slight atrophy of midline cerebellar structures is commonly observed during the course of the disease (see Strupp et al., 2007). Altered percept therefore seems very unlikely to be caused by extra-cerebellar modifications.

The general concern about comparing patients to healthy controls can be met by the fact that our paradigm included an additional control within the patients group. That the altered response in patients was only observed after valid adaptation (100% coherence) whereas there was no change in judgment compared to healthy controls after invalid adaptation (0% coherence) clearly argues for an effect specific for a certain visual stimulation and not a general group effect.

The same argument is capable to dispel the concern that the observed difference between patients and controls reflects changes in the capability to produce the required motor response. Cerebellar patients often suffer pronounced motor deficits and cognitive tasks might be impaired if the required motor output is so demanding that patients show motor response deficiencies (Ravizza and Ivry, 2001). That the group differences measured were due to difficulties with the motor task is in our case very unlikely. Firstly, only a button press was required within no time limitation and secondly if the difficulty would have had any influence on the produced answer this effect should have been observed in both, the test (“MAE”) and the control (“no-MAE”) condition. Only differences between groups in the test condition where motion adaptation was induced were observed. No significant difference between patients and controls were observed concerning the control condition. Additionally, since the extent of the MAE was calculated as the difference between the test and the control condition any influence of a possible bias due to a preferred or unaffected hand is excluded.

Other motor acts which might take part in the observed perceptual deviance of cerebellar patients are eye movements. Beside deficits in saccade accuracy, as indicated by increased position errors and a larger number of corrective saccades shown for human and non-human primates after cerebellar damage (Vilis and Hore, 1981; Waespe and Baumgartner, 1992; Tagaki et al., 1998; Barash et al., 1999), also fixation can be impaired in cerebellar patients due to nystagmus. However, as described in the methods, patients suffering from nystagmus, which is a rapid involuntary rhythmic eye movement, were excluded from the study. The eye movements of the remaining patients were analyzed carefully and it was shown that deviations from the fixation point were not related to motion adaptation and the perceptual judgment. This is in line with findings by Nawrot and Rizzo (1998) who also reported no deficit in fixation for their group of cerebellar patients despite visual perceptual impairments. In our study also number and velocity of saccades were tested and showed neither a relation to motion adaptation nor to the perceptual judgment. Results so far therefore clearly argue against an influence of movement execution in the generation of the MAE. But how could the cerebellum influence the perception of illusionary motion?

The first attempt to interpret the difference in the MAE between cerebellar patients and healthy controls refers to the well established deficit in perceiving the direction of motion

stimuli with low motion coherence, observed after cerebellar lesions (Ivry and Diener, 1991; Nawrot and Rizzo, 1995, 1998; Thier et al. 1999, Jockisch et al., 2005). As a consequence of the impaired perception of real motion also the perception of illusionary motion might be altered. However, in our study the ability to perceive the direction of real motion was not linked to the perceptual judgment of the MAE i.e. there was no correlation between the two judgments. One could argue that the parameters chosen, e.g. presentation time and location, were not fit to disclose subtle motion perception deficits, however, there are also other arguments strongly disapproving a simple connection between a general deficit in motion perception and the altered MAE: The MAE induced under fixation is typically thought to result from the direct adaptation of mechanisms sensitive to retinal image movement (Anstis et al., 1998). If the processing of the adapting stimulus is decreased due to cerebellar impairment a decreased MAE might result. This idea is not supported by the perceptual findings since first of all 4 out of 5 patients exhibiting an altered MAE showed an increase in MAE and secondly because the perception of motion is only impaired if the presented stimulus contains signal as well as noise (incoherent motion). The adaptation stimulus in this paradigm, however, was comprised of coherent motion, i.e. only signal. Also the possibility that an impaired judgment of the noisy test stimulus led to the differences between cerebellar patients and controls is not supported. If no motion is perceived the decision about two directions is normally made with a 50% chance level. Therefore, also in this case a reduced MAE (close to zero) would result. However, as pointed out above, 4 out of 5 patients showed an increased MAE, i.e. a judgment further away from chance level. Again, a response bias added to the 50% chance level can be excluded since the effect was confined to one condition only. Reduced processing of the real motion signal can therefore hardly explain the altered MAE and changes in perception of real and illusionary motion seem to be induced by the cerebellum, however, via different loops of cerebellar-cortical interactions.

As stated in the introduction one function of the cerebellum is believed to be the storage of the prediction of sensory input induced by self movement. Such a sensory prediction can lead to the percept of illusionary motion. Haarmeier et al. (2001) showed that the prediction of the visual consequences of smooth-pursuit eye movements could be modulated by repeatedly showing a non stationary background stimulus during the execution of the pursuit eye movement. After adaptation perception during smooth pursuit was modulated in such a way that stationary background stimuli were judged as moving opposite to the direction of the adaptation stimulus. This could be shown for adaptation in the same or opposite direction of the pursuit eye movements.

If the concept of predicting sensory consequences during self movement is extended to a sensory prediction during distinct motor states a similar idea is applicable to visual motion illusion under fixation. Prolonged motion stimulation during a distinct motor state, i.e. fixation, might alter the expectation of the sensory consequences during this state. Dependent on the alteration, impaired cerebellar processing might lead to a changed MAE: If e.g. the sensory prediction has ceased to be adapted no MAE should be observed. If on the other hand the sensory expectation is strongly adapted a very pronounced MAE should be seen. This idea is in principle compatible with our data since 4 out of 11 patients showed an increased MAE compared to controls whereas one patient showed a significant decrease, namely a MAE close to zero.

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Curriculum vitae

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Händel B, Lutzenberger W, Thier P, Haarmeier T. Selective attention increases the dependency of cortical responses on visual motion coherence in man. submitted

Händel B, Haarmeier T. Cross-frequency coupling of brain oscillations indicates the success in visual motion discrimination. submitted

Händel B, Lutzenberger W, Thier P, Haarmeier T. Deficits in visual motion perception due to cerebellar lesions are paralleled by changes in motion coherence specific cortical response modulation. in preparation

Händel B, Lutzenberger W, Thier P, Haarmeier T. Neuromagnetic activity, including RMS values, delta and alpha oscillations, differentiates between correctly and incorrectly perceived visual motion. in preparation

Händel B, Pomper J, Thier P, Haarmeier T. Altered motion aftereffect in patients with cerebellar lesions. in preparation

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