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Research Article

fMRI Response During Visual Motion Stimulation in Patients with Late Whiplash Syndrome

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After whiplash trauma, up to one fourth of patients develop chronic symptoms including head and neck pain and cognitive disturbances. Resting perfusion single-photon-emission computed tomography (SPECT) found decreased temporoparietooccipital tracer uptake among these long-term symptomatic patients with late whiplash syndrome. As MT/MST (V5/V5a) are located in that area, this study addressed the question whether these patients show impairments in visual motion perception. We examined five symptomatic patients with late whiplash syndrome, five asymptomatic patients after whiplash trauma, and a control group of seven volunteers without the history of trauma. Tests for visual motion perception and functional magnetic resonance imaging (fMRI) measurements during visual motion stimulation were performed. Symptomatic patients showed a significant reduction in their ability to perceive coherent visual motion compared with controls, whereas the asymptomatic patients did not show this effect. fMRI activation was similar during random dot motion in all three groups, but was significantly decreased during coherent dot motion in the symptomatic patients compared with the other two groups. Reduced psychophysical motion performance and reduced fMRI responses in symptomatic patients with late whiplash syndrome both point to a functional impairment in cortical areas sensitive to coherent motion. Larger studies are needed to confirm these clinical and functional imaging results to provide a possible additional diagnostic criterion for the evaluation of patients with late whiplash syndrome. **Key Words:** Whiplash—fMRI—Visual motion perception.

Whiplash injuries are caused by a sudden acceleration of the trunk with hyperextension, hyperflexion, or hyperlateroversion of the neck. The symptoms experienced by these patients vary from neck pain, headache, vertigo, nausea, to emotional and cognitive disturbances, especially in concentration and attentional processing (1). In 1-year follow-up studies, some authors (2, 3) have reported that up to 24% of these patients develop chronic symptoms. Patients with whiplash injuries also exhibit reduced reading capabilities due to disturbed oculomotor control (4).

Resting perfusion single-photon-emission computed tomography (SPECT) and positron emission tomography (PET) found decreased temporoparietooccipital (TPO) tracer uptake among long-term symptomatic patients with late whiplash syndrome (5–8). Interestingly, this decreased resting perfusion in SPECT imaging was found both in chronic symptomatic and asymptomatic persons with a history of whiplash trauma. The underlying pathophysiologic process remains largely unknown (9).

The TPO region has been shown to be one of the important cortical sites of visual motion processing. The

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results of PET and functional magnetic resonance imaging (fMRI) studies in healthy subjects who viewed motion displays indicate that the human homolog of the motion-selective areas MT (middle temporal) and MST (middle superior temporal), which are also referred to as the fifth visual area and its adjacent area (V5/V5a) in monkeys, are located in that region (10–15). To explore whether dysfunction of this cortical region might correlate with some of the symptoms of late whiplash syndrome, we addressed following issues:

1. Is motion perception impaired in patients with late whiplash syndrome?
2. Is the fMRI response to visual motion stimulation altered in the TPO region?
3. Are there differences between symptomatic patients with late whiplash syndrome and asymptomatic patients after whiplash trauma?
4. Is there a correlation between motion perception and fMRI results?

We measured visual motion perception with a well-established psychophysical test and fMRI in symptomatic patients with late whiplash syndrome, in asymptomatic patients after whiplash trauma and in a control group without history of trauma. To exclude macroscopic brain damage a T_2-weighted MRI of the brain was also performed.

Methods

Clinical testing of visual motion perception was performed in patients and volunteers on a Mac 7600 computer. The display program produced animated sequences of 60 sparsely spaced black dots on a medium grey background (mean luminance, 30 cd/m^2). The motion sequences were designed to simulate frontoparallel motion within two fields (5 × 5 degrees). The dot motion had a constant speed of 6 degrees/s. One field of dots was positioned in the left visual field, and the other was presented in the right visual field (see inset in Fig. 1). One field contained dots with random directions, whereas the other field contained dots with a mixture of random and coherent directions (left or right). Eight levels of motion coherence were presented in a random order. The coherent motion was randomly added to the left or right motion field. The subjects were asked to fixate on a central fixation spot and to report which of the two fields contained coherent motion (i.e., detection). Viewing distance was fixed at 0.57 m with the help of a chin-rest. Each trial consisted of a 0.5-s period in which both fields were simultaneously presented. The subject responded in a two-alternative forced-choice paradigm: which field contained the coherently moving dots. The investigator was blind with respect to the patients' and volunteers' history. All subjects were given a few trials to become acquainted with the task and the stimulus displays. They were instructed to maintain fixation throughout each trial and to respond quickly.

fMRI was performed in a separate session on another day with a 1.5-T Siemens Magnetom Vision using T_{2*}-weighted echo planar imaging (TE, 70 ms; flip angle, 90 degrees; FOV, 250 mm; matrix, 128 × 128; 12 contiguous 5-mm slices, resulting in a voxel size of 1.95 × 1.95 × 5 mm. Slice orientation was positioned oblique to the axial plane through the striate and extrastriate visual cortices). A 3-D high-resolution data set was performed using a T_1-weighted MP-Rage (magnetization-prepared, rapid acquisition gradient echo) sequence with a 1 × 1 × 1-mm voxel size. This anatomic data set was used to normalize and transform the functional data of each individual subject into the Talairach space (16). We used the software package BrainTools by Krish Singh (17) to analyze the functional data. This included 2-D motion correction, coregistration, normalization, and smoothing with a gaussian filter (SD, 2 voxels).

To minimize head motion, the subject's head was fixed using a vacuum cap. Residual in-plane motion was corrected by applying an image-correction algorithm (18). In two cases, excessive out-of-plane motion was detected, and the entire examinations of these two patients were excluded from further analysis. During the MRI sessions, subjects viewed the stimuli through a plexiglass prism that was positioned directly above the window of the Siemens headcoil. The stimuli were created on a Macintosh computer and back-projected onto a translucent screen within the gantry using a LCD Projector (Sony). The image subtended 60 degrees in width and 30 degrees in height (corresponding to 180 × 90 pixels on the display). The stimulation protocol consisted of twelve 50-s intervals. Within each interval, ten volumes were acquired. A baseline resting period (fixation point and static dots) alternated with either a period of randomly moving dots (stimulation 1) or a period of coherently moving dots (stimulation 2). Dot motion was constant at 6 degrees/s. During the coherent motion condition, the coherence level was constant at 90%. Both fMRI experiments in each patient were performed during the same session. In the first experiment, the subjects were instructed to maintain fixation throughout the run. In the second experiment, subjects were asked to pursue with their eyes the coherently moving dots. The order of the experiments was kept constant, to exclude additional variation within the groups due to habituation effects.

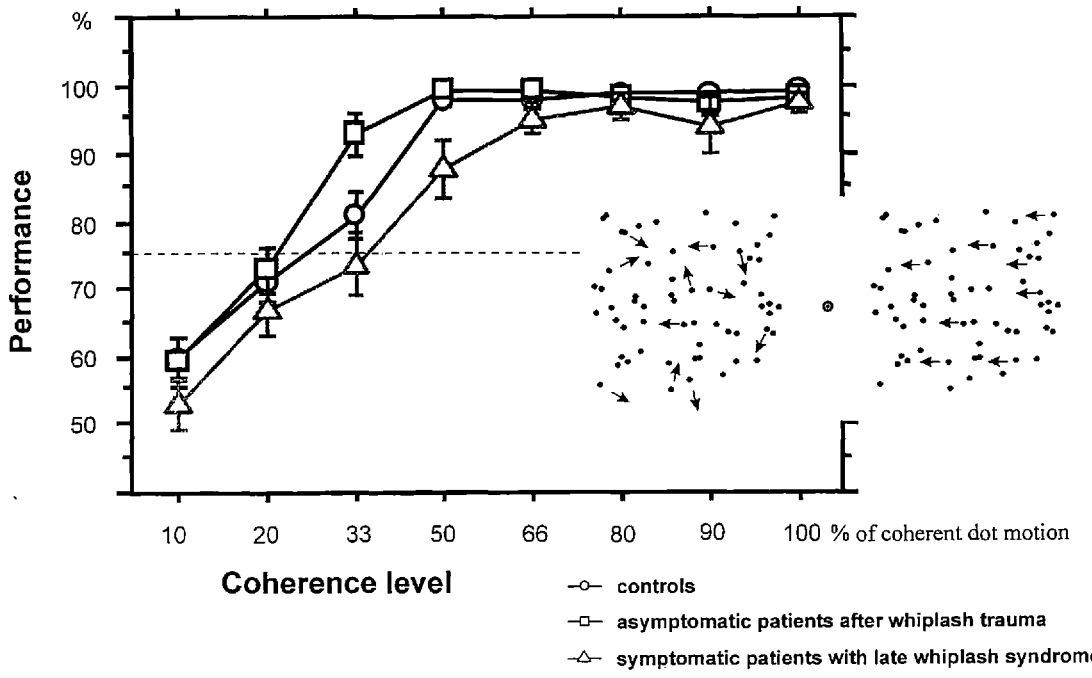

Figure 1. Results of psychophysical estimate of coherent motion thresholds. The inset demonstrates an example of the display for the psychophysical testing of visual motion perception. The error bars show the 95% confidence interval; the dashed line represents 75% correct performance.

Eye movements were monitored with MR-compatible electrooculogram (EOG) (19). Patients and volunteers who did not follow the instructions could thus be excluded. Two patients were excluded from the study, either owing to excessive head motion, to compliance problems, or to both.

The study was approved by the local ethics committee, and all subjects gave written informed consent.

Subjects

The studies of five patients (age, 31–58 years; mean, 43.2 years) with late whiplash syndrome grade II Quebec Classification (20) could be evaluated. The illness duration was 14–34 months (mean, 26.2 months). All patients were unable to work (inclusion criteria), and all were investigated with a neuropsychological test battery. The symptoms of the patients included cervicalgia, headache, cognitive disturbances, and lumbovertebral symptoms. All patients were highly motivated in further investigation of their complaints and thus interested in the performed experiments.

Five asymptomatic patients after whiplash trauma (age, 31–45 years; mean, 33.2 years) but without any persisting symptoms or restrictions in daily life were also studied.

Seven healthy volunteers without history of trauma (age, 27–53 years; mean, 35.0 years) formed the control group. These subjects were recruited from the hospital staff.

Patients and volunteers were naive with regards to the experimental aims and fMRI methods. The experimenter (M.W.G.) was blind with respect to the group classification of the subjects during psychophysical testing.

Exclusion criteria were as follows: Any medication interfering with central nervous system (CNS) function 24 h before each examination; any other medical or neurologic disease interfering with CNS function; or any psychiatric, otologic, or ophthalmologic disorders (as determined by standard screening procedures).

Data Analysis

Psychometric functions, relating performance to coherence level, and coherent motion thresholds (75% performance level) were calculated. An analysis of variance (ANOVA) was conducted on the performance data to determine the effects of experimental group, coherence

level, hemisphere, and task. In the fMRI experiments, the time course of significantly activated clusters was inspected and compared with the stimulus time course. BOLD response levels in regions-of-interest (ROI) in V5 on each hemisphere were determined across the different stimulus conditions, tasks, and groups respectively. The ROI was determined based on anatomic and functional landmarks in the T1 and activation images. Once the ROI was positioned in each hemisphere, its location was constant over all measurements. The values entered into the ANOVA are based on the average BOLD signal (SD of voxel time course × normal correlation coefficient) without a threshold.

Results

Diagnostic whole brain T_2-weighted MRI of all patients and volunteers showed no evidence of structural damage.

Coherent Motion Thresholds

The results of the psychophysical measurements of coherent motion perception are shown in Fig. 1. Compared with the controls, symptomatic patients required a significantly larger portion of coherently moving dots to detect the coherent motion. There were no significant differences between the volunteers and asymptomatic patients after whiplash trauma (Fig. 1). If anything, the asymptomatic patients tended to perform slightly better than the control subjects. The mean threshold levels corresponded to 33%, 20%, and 25% coherence level for 75% correct performance in the symptomatic and asymptomatic patients and the control subjects, respectively. We found no effects of hemifield (left or right visual field) or stimulus direction (leftward or rightward).

fMRI Findings

With EOG we typically observed some eye blinks occurring with a similar frequency for baseline and stimulation periods during the fMRI experiments for patients and volunteers. The EOG traces indicated that all subjects followed the instructions (fixation and pursuit). During fixation, we did not find significant optokinetic nystagmus during the motion stimulation, suggesting that the patients and controls could suppress reflexive eye movements. Compared with the other two groups, the symptomatic patients, however, showed a tendency to exhibit saccadic pursuit during the smooth pursuit task.

The fMRI activity in the region of interest of the MT/MST area during visual motion perception random dot motion versus stationary dots showed no significant difference between all three groups ($F_{2, 16} = 0.51$; NS). All subjects in each of the three groups showed significant activation levels in the MT/MST region during random dot motion, but this activation level does not significantly differ across groups.

The results of the ROI analysis of the coherent motion comparisons are shown in Fig. 2 separately for the condition requiring fixation (left half) and the condition requiring pursuit (right half). The mean BOLD responses in the MT/MST region during coherent motion perception with fixation revealed a significant increase in each group compared with the condition with random dot motion, but the level of increase varied between symptomatic patients and controls but not between asymptomatic patients and controls (Fig. 2). This trend resulted in a significant difference ($p = 0.037$) in the fMRI response during coherent motion perception between symptomatic patients and the other two groups. Using the Scheffé test for post hoc pairwise comparisons, we could confirm that the difference arose between the symptomatic patients and the other two groups (for each comparison, $p < 0.05$). There was also an increase of the fMRI activity in the ROI of the MT/MST area between fixation and pursuit of the coherent dot motion in each group. This replicates an earlier fMRI study of our group in healthy volunteers regarding the fMRI activity changes and the location of the V5/V5a complex (19). The BOLD response was significantly lower in the symptomatic patients with late whiplash syndrome compared with the asymptomatic patients or with the control group.

The ANOVA revealed significant main effects for the following factors. The main effect of group (symptomatic, asymptomatic, and controls) was significant for the ROI over MT/MST (V5/V5a) during coherent motion perception ($F_{2, 16} = 4.6$; $p < 0.05$). The difference was mainly related to the difference between symptomatic patients and the control group (Scheffé pairwise post hoc comparisons). The main effect of task (fixation or pursuit) was also significant ($F_{1, 33} = 7.9$; $p < 0.01$). The main effect of stimulus condition (random noise vs. coherent motion during fixation) was not significant.

On an individual basis (across groups), the comparison between age and fMRI response in MT/MST (V5/V5a) during random dot motion and coherent motion showed no significant correlation. Also the age differences between groups were not significant. There were no significant gender differences in the fMRI results.

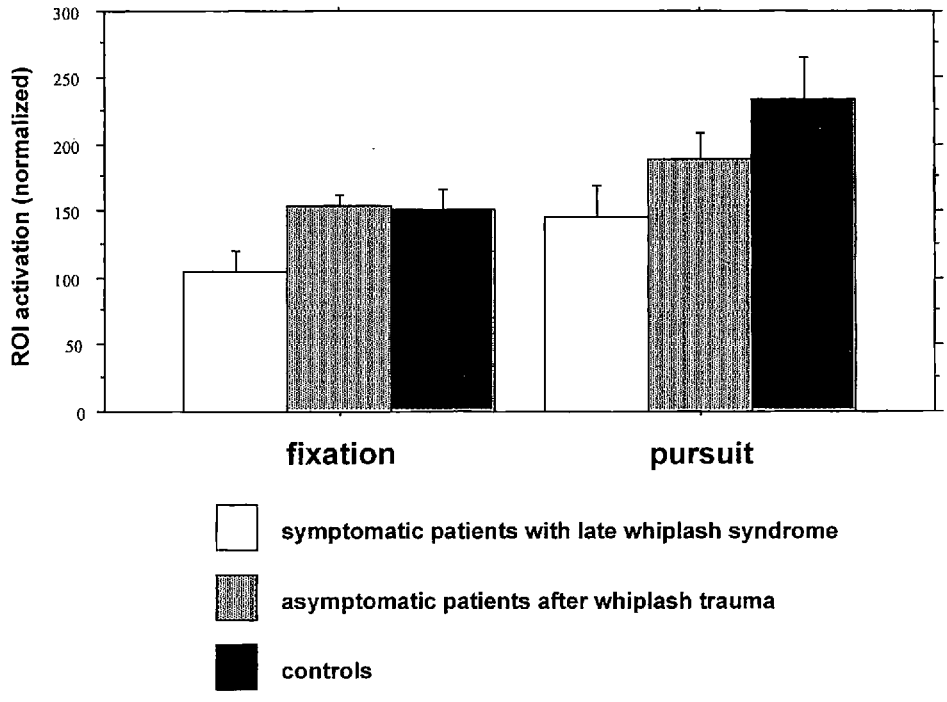

Figure 2. Functional magnetic resonance imaging (fMRI) results of the region of interest (ROI) analysis in V5 for the condition coherent dot motion with fixation or pursuit (averaged over both hemispheres). The error bars show the 95% confidence interval.

Discussion

There is an ongoing debate whether whiplash is a valid injury or a cultural phenomenon (21–24). Objective findings are needed and could help the patients to understand their symptoms better.

In this study, symptomatic patients with late whiplash syndrome showed a significantly decreased performance in psychophysical tasks of coherent motion detection and corresponding fMRI activation in MT/MST compared with asymptomatic patients after a whiplash trauma and with healthy volunteers. These findings are in contrast to the nuclear imaging studies of Otte (5–8), who found decreased resting perfusion HMPAO-SPECT in the TPO region in symptomatic and asymptomatic patients after whiplash trauma. The results of these SPECT findings in the TPO region in whiplash patients have also recently been placed in question by Bicik et al. (25). In their resting perfusion [^{18}F]glucose PET and HMPAO-SPECT study, they found no parietotemporal perfusion deficit in patients with late whiplash syndrome compared with controls. In a study with patients after traumatic brain injuries, Ichise et al. (26) found with HMPAO-SPECT temporal perfusion abnormalities in 40%, but only in 5% parietal and in 2% occipital perfusion deficits. It should be noted that all SPECT data were acquired during rest, whereas the fMRI result is based on the difference between the resting and activated state, and as such, they are not directly comparable.

Although we did not find differences between asymptomatic patients and controls, we found significantly less fMRI activation in the MT/MST complex in patients with late whiplash syndrome. The decreased performance in visual motion perception and fMRI response during coherent visual motion perception in symptomatic patients with late whiplash syndrome reported here suggests that a functional impairment in this extrastriate visual area is evident.

The ability to focus attention on objects in the peripheral visual field might also be impaired in late whiplash syndrome. Impaired visual attention could, in part, underlie the increased thresholds for coherent motion shown by the symptomatic patients. During the fMRI experiment, the coherent motion paradigm was interleaved with stationary dots and random dot motion during the fixation and pursuit task. There was no significant difference of the fMRI activity between patients and volunteers in the random dot motion perception condition. This serves as a control condition that speaks against substantial attentional effects across groups.

In a previous study (19), we reported an increase in fMRI response during pursuit compared with a fixation task. Other studies without eye movements showed the attentional influence on the fMRI activation during visual perception (27–29), so that the increase in our study is at least partly due to an attentional effect. Our patients with late whiplash syndrome reported difficulties following the coherent moving dots during the pursuit task. Their difficulty in pursuit was also evident in the EOG recordings. This reduced capability to perform smooth pursuit eye movements might influence the fMRI results in the pursuit condition. However, differences in the fMRI response were also evident during the fixation task, which could be done properly by all subjects. The significantly reduced fMRI response of the symptomatic patients in the fixation and pursuit task points to a perception deficit. Disturbed eye-movement control could thus be a consequence of this perceptual impairment. Impaired control of saccadic eye movements during reading and pursuit eye movements (4) have also been reported in patients with late whiplash syndrome.

Lesions of the TPO region have been shown to impair visual motion processing (30–33) and reduce the gain of pursuit (34, 35). In our study, macroscopic brain damage was ruled out with diagnostic brain MRI. Thus, the disturbed motion processing revealed in symptomatic whiplash patients might be a consequence of microscopic damage within the cortical region or to the disconnection of projections from and into these motion-sensitive areas. Otherwise, although highly motivated, these patients experienced ongoing pain, and some of them, anxiety or depression. These symptoms might also lead to sleep disturbances. The possible influence of this on specific task-related activities is unknown.

For technical reasons, we were unable to perform whole-brain fMRI. However, within the scanned volume, we could not detect significant BOLD responses in other brain areas. Functional impairment of other brain areas, connected to MT/MST, but outside of the acquired volume, might be the origin of the observed differences between our patient groups.

In conclusion, using fMRI and psychophysical tests of motion perception, it was possible to observe differences between chronic symptomatic and asymptomatic patients after whiplash trauma. These results suggest an impairment in the MT/MST (V5/V5a) region with respect to motion processing. Microscopic structural and primary or secondary functional impairment cannot be differentiated in this study. Further studies with whole-brain fMRI should investigate larger groups of patients after whiplash trauma as well as other chronic diseases to evaluate the diagnostic relevance of fMRI or clinical psychophysical testing of visual motion perception to find a valid tool in diagnostic process in patients with late whiplash syndrome.

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