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Disturbed overt but normal covert shifts of attention in adult cerebellar patients

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In an attempt to provide a common denominator for cognitive deficits observed in cerebellar patients, it has been suggested that they might be secondary to impaired control of attention, a 'dysmetria of attention', conceptually analogous to motor dysmetria. Albeit appealing and quite influential, the concept of attentional dysmetria as a consequence of cerebellar disease remains controversial. In an attempt to test this concept in a direct way, we compared the performance of patients with cerebellar disorders to that of normal controls on tasks requiring either overt or covert shifts of spatial attention. In the first experiment, visually guided saccades, i.e. overt shifts of spatial attention, were elicited. In the second experiment, covert shifts of attention were evoked by the need to discriminate the orientation of a Landolt C observed during controlled fixation and presented in the same locations as the saccade targets in the previous experiment. The allocation of attention was assessed by comparing acuity thresholds determined with and without spatial cueing. The patients exhibited dysmetric saccades as reflected by larger absolute position errors or a higher number of corrective saccades compared to controls. In contrast, the ability to shift attention covertly was unimpaired in the patients, as indicated by a robust improvement in visual acuity induced by spatial cueing which did not differ from the one observed in the controls and which was independent of the range of SOAs (stimulus onset asynchronies) tested. Finally, the individual amount of saccadic dysmetria did not correlate with the individual performance in the covert attentional paradigm. In summary, we conclude that the contributions of the cerebellum to attention are confined to overt manifestations based on goal-directed eye movements.

Keywords: cerebellum; saccades; attention; dysmetria; psychophysics

Abbreviations: CNS = central nervous system; IDCA = idiopathic cerebellar ataxia; ISI = interstimulus interval; PUS = peripheral nervous system; SCA = spinocerebellar atrophy; SOA = stimulus onset asynchrony

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Introduction

The traditional view that the function of the cerebellum is limited to motor control has been challenged recently by research suggesting that the cerebellum might contribute to a wide range of non-motor processes including cognitive functions as well (Leiner *et al.*, 1986, 1993; Schmahmann, 1991, 1993; Daum and Ackermann, 1995; Fiez, 1996; Schmahmann and Sherman, 1998). One piece of evidence supporting the view of cerebellar contributions to cognition is the consistent demonstration by different laboratories of impairments in patients with cerebellar lesions on a number of visual tasks requiring the judgement of visual motion (Ivry and Keele, 1989; Ivry and Diener, 1991; Nawrot and Rizzo, 1995; Ivry, 1997; Thier *et al.*, 1999). Its underlying cause remains unknown. In view of the uniformity of the cerebellar microcircuitry suggesting a corresponding computational uniformity, various attempts have been made to single out a common functional principle helping to explain how the cerebellum might influence motor as well as non-motor behaviour.

Among these hypothetical explanations, the possibility that the cerebellum might be involved in the control of spatial attention is notably appealing. The reason is that the cerebellum is one of the key structures in the control of saccades (for a review see Robinson and Fuchs, 2001). Saccades are overt

manifestations of spatial shifts of attention: by moving the image of a peripheral object onto the fovea, saccades make accessible the advantages of foveal vision and thus enable us to focus our analysis of visual information onto behaviourally crucial elements of the input, thereby optimizing the use of capacity-limited resources. This process of assigning priority to some sensory stimulation over others is the hallmark of any definition of attention. Moreover, different studies (i.e. Rizzolatti *et al.*, 1987; Shelgia *et al.*, 1994; Deubel *et al.*, 1996) have demonstrated that saccades and shifts of spatial visual attention are coupled in an obligatory manner. Lesions of the cerebellum do not abolish saccadic eye movements, but they make them inaccurate in space and time, and much more variable (Barash *et al.*, 1999). A deficit analogous to the dysmetria of overt shifts of attention might also pertain to the reallocation of spatial attention based on covert shifts of spatial attention in the visual field, while keeping the eyes still. Specifically, lesions of the cerebellum might lead to attential dysmetria, i.e. slowed, less precise and more variable shifts of the 'focus of attention', thereby hampering the visual analysis of objects in the visual field. Experimental support for a contribution of the cerebellum to spatial and other forms of attention has come from studies assessing the control of attention in patients with cerebellar lesions due to acquired neurological damage or due to infantile autism, the latter a developmental disorder reported to be associated with anatomical abnormalities of the cerebellum (Courchesne *et al.*, 1988, 1994*a*, *c*). Attentional deficits have been observed in both groups of patients and for two different types of tasks. A first type of deficit has been reported for detection tasks remaining in one sensory modality (visual or auditory) under focused attentional conditions or for tasks requiring rapid and accurate shifts of attention between auditory and visual stimuli (Akshoomoff and Courchesne, 1992, 1994; Courchesne *et al.*, 1994*b*). A second one has been shown for tasks requiring the shift of spatial attention prompted by spatially accurate cues in visual detection or visual discrimination paradigms (Townsend *et al.*, 1996, 1999). These findings, however, have been challenged by other studies which failed to demonstrate attention deficits resulting from cerebellar disorders (Helmuth *et al.*, 1997; Schoch *et al.*, 2004). Moreover, recent work has provided evidence that the deficits in switching attentional set observed in some of the studies might actually have been due to difficulties in response reassignment rather than disturbances in the control of attention because the deficits turned out to depend on the complexity of the motor task (Ravizza and Ivry, 2001; Bischoff-Grethe *et al.*, 2002). Similar to these behavioural studies, functional imaging studies have yielded contradictory results, with some studies showing cerebellar acitivations depending on attention (Allen *et al.*, 1997) while others failed to demonstrate cerebellar reponses during covert shifts of spatial attention (e.g. Corbetta *et al.*, 1998).

The goal of the present study was to resolve this controversy. Towards this end, we directly compared the performance of patients with cerebellar degeneration or acquired cerebellar lesions on tasks requiring overt and covert shifts of spatial attention. Importantly and differently from previous studies, eye movements were rigorously controlled in this study in order to rule out that visual discrimination was influenced by eye movement disturbances. In essence, we demonstrate that the patients exhibit significant saccade dysmetria but have normal shifts of covert attention. These results suggest that the cerebellum does not contribute to spatial orienting unless overt goal-directed eye movements are engaged.

Methods

Subjects

Thirteen patients participated in the study (five females and eight males; mean age 45 years, range 26–70). All patients suffered from neurological diseases which were confined to the cerebellum, as suggested by thorough clinical examination and cerebral MRI scans. Eight patients exhibited cerebellar atrophy, with six of them suffering from a global cerebellar atrophy and the remaining two showing atrophy confined to the cerebellar vermis. Five patients had focal cerebellar lesions located in one of the cerebellar hemispheres. Neurological diagnoses of the patients showing cerebellar atrophy were: spinocerebellar atrophy type 6 (SCA 6; $n = 2$), SCA 7 ($n = 1$), idiopathic cerebellar ataxia (IDCA; $n = 3$), gluten-associated cerebellar atrophy ($n = 1$) and Gerstmann–Sträußler–Scheinker disease ($n = 1$). The group of patients with focal cerebellar hemispheric lesions comprised the following subjects: four patients with an ischemic lesion in the PICA distribution region (two on the right and two on the left side) and one patient with a medulloblastoma located in the right cerebellar hemisphere. Analyses were performed for the whole group and, in a second step, for two subgroups, the first comprising patients with cerebellar atrophy and the second comprising patients with damage restricted to the lateral cerebellar hemispheres.

Normal control subjects, matched to the age of the individual patients (five females, eight males; mean age 46 years, range 26–66) were recruited from the clinical staff or from the pool of patients in our clinic with diseases of the PNS but no oculomotor or CNS disorder; they did not receive centrally acting medications. A further group of normal subjects ($n = 7$; one female, six males) was recruited for a separate experiment (experiment 3), with the mean age being 30 years (range 27–35).

Patients and control subjects suffering from refractive errors wore their glasses during testing. Informed consent was obtained from all patients and control 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.

Experimental paradigms

All experiments were performed in a dimly lit room. Stimuli were generated by a Silicon graphics workstation and presented on a 19 inch computer monitor (Mitsubishi, frame rate 72 Hz, 1280 × 1024 pixels). Subjects underwent the experiments at a fixed viewing distance of 57 cm (saccade task) or 80 cm (acuity task), respectively. In each individual trial, eye movements were recorded at a sampling rate of 200 Hz using an infrared Limbus eyetracker (Am Tech®, Weinheim, Germany). Head movements were minimized by means of a bite board. The eye position was fed back to the workstation which also controlled the visual stimulation, thus allowing for online control of fixation (see below). In addition, eye position

records were stored and analysed off-line on a single trial basis after correcting for a baseline of 500 ms of central fixation before target (or cue) onset as specified in the following sections.

Experiment 1: overt shifts of spatial attention in patients with cerebellar damage and controls—comparison of visually guided saccades

Three hundred visually guided horizontal saccades were elicited by targets appearing either left or right of a central fixation point at an eccentricity of 9°. Single trials started with the presentation of a central green fixation point (diameter 10 min of arc, luminance 3.5 cd/m^2) on a grey background (0.2 cd/m^2). After a 500 ms period of central fixation, a white target (diameter 10 min of an arc, 5.5 cd/m^2) appeared either 9° right or 9° left of the fixation point and remained visible for 500 ms (Fig. 1A). Trials with saccades to the right and left were randomly interleaved, with the intertrial interval being 1500 ms. Horizontal and vertical eye position were recorded for a time interval starting 500 ms before target onset until 750 ms after target offset. The records were stored on the disc of the workstation which also controlled the presentation of the stimuli and analysed off-line on a single trial basis after baseline correction based on a 500 ms period of central fixation preceding the target presentation. As none of the subjects exhibited any significant asymmetry in saccade performance, saccades to the left and to the right were pooled for analysis. Saccades were detected by a threshold criterion in the velocity domain applied to the horizontal eye position recordings. In order to characterize the precision and metrics of the saccades, both horizontal and vertical eye positions were considered. The following parameters were determined for each single trial and then averaged for the individual subject. First, the amplitude and latency of the first saccade were calculated. Secondly, the mean absolute position error after the first saccade was determined, i.e. the absolute value of the difference between eye position and target position derived from a 20 ms interval after the end of the first saccade. This second measure provides a more accurate estimate of saccadic dysmetria than mean saccade amplitude because hypometric and hypermetric saccades may, in principle, cancel each other out in individual subjects or in a group of subjects. As a further and more indirect estimate of saccadic dysmetria, the frequency of corrective saccades was assessed. To this end, the number of saccades following the initial gaze shift were counted for all trials for the 750 ms period of target presentation and were then expressed as the mean number (frequency) of corrective saccades during one target presentation. Finally, post-saccadic drift, i.e. post-saccadic eye velocity determined for a 100 ms time interval starting 20 ms after the end of the first saccade, and the skewness of saccades given as the difference between the time necessary to reach maximal and the time to regain minimal eye velocity divided by the total duration of the saccade were calculated. All the oculomotor parameters addressed were tested for significant differences ($P < 0.05$) between the patient and control group applying one-way analysis of variance (ANOVA).

Experiment 2: comparison of covert shifts of spatial attention in patients with cerebellar damage and controls

In this experiment and in experiment 3, the ability to shift spatial attention covertly was estimated from the difference in acuity thresholds determined in the presence and absence of a spatial cue, respectively. Acuity thresholds were measured in the peripheral visual field based on a paradigm requiring the discrimination of two possible orientations of a conventional Landolt C optotype (gap = one-fifth of the outer diameter of the Landolt C).

Single trials (Fig. 1B) started with the presentation of a central red fixation point (10 min of arc, 2 cd/m^2) on an otherwise black background (0.05 cd/m^2). In trials with a spatial cue (50% of all trials), a white dot (20 min of arc, 6.2 cd/m^2, presentation time 100 ms) was presented at one of two possible locations, following a 500 ms period of successful fixation as defined by eye positions falling within a square of 2.25° side length centred around the fixation point. In order to allow for a direct comparison with the performance in the saccade task, the cue appeared either 9° left or right of the fixation point. After an interstimulus interval (ISI) of variable duration (see below), a white Landolt C (6.2 cd/m^2, gap orientation either at the top or at the bottom), i.e. the discriminandum, was presented for 150 ms at the location of the prior cue, i.e. the cue always indicated the true position of the Landolt C (valid cue). In the second half of trials, the no cue trials, the Landolt C presentation started immediately after the 500 ms period of maintained fixation. Trials with different cue and position conditions were presented randomly

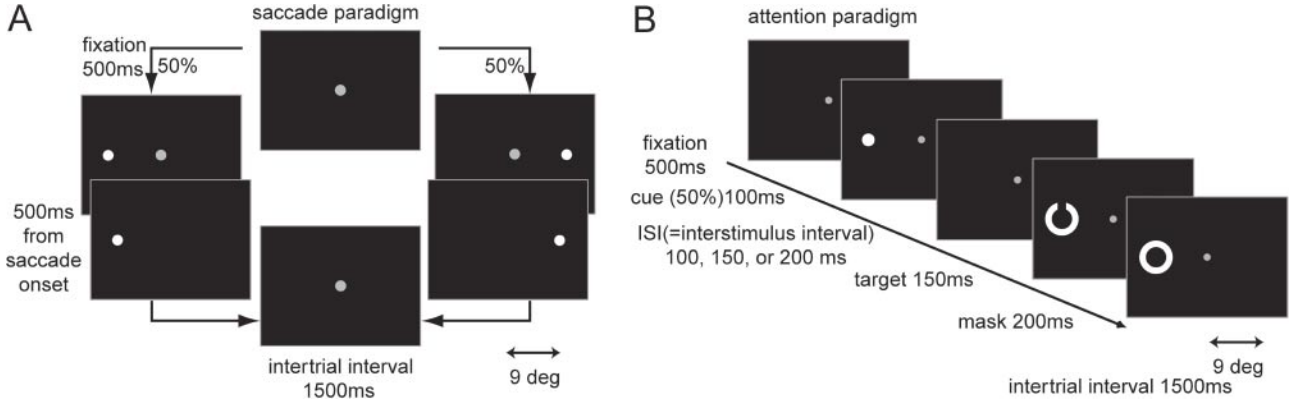

Fig. 1 Stimulus sequence in the patient study. (**A**) Saccade paradigm. Single trials started with the appearance of the central fixation dot (500 ms) followed by the saccade target presented 9° either right or left of the fixation point. (**B**) Attention paradigm. After 500 ms of stable central fixation, a Landolt optotype was presented which was announced in cue trials by a white dot located at the same position as the Landolt C (valid cue trial shown here). The Landolt C, and thus also the cue, could appear in one of two locations. The ISI (i.e. time interval between cue offset and target onset) was varied in three separate experiments. Attentional effects were defined as the difference between acuity thresholds observed for the valid and the no cue condition (50% of trials, each).

interleaved within one block. In order to avoid the analysis of afterimages, the gap of the Landolt C was closed by a mask visible for 200 ms. A new trial started after an intertrial interval of 1500 ms.

Subjects were informed that in some trials a white dot would indicate the location of the following Landolt C. They were instructed to maintain fixation of the central red dot and to indicate which of the two possible gap orientations had been presented by pressing one of two possible buttons (two alternative forced choice task). Pressing the button grasped by their right hand corresponded to a gap at the top, and pressing the left button indicated a gap at the bottom. Subjects were guided to answer as accurately as possible, not as fast as possible. Responses released within a time interval of 2000 ms after the disappearance of the discriminandum were accepted. Positive feedback, indicating that the subjects had fulfilled the task requirements, was given by means of a short beep. In addition, negative feedback (two consecutive short beeps) was delivered when the eye position had surpassed the borders of the fixation window at any time during the trial. Such trials were excluded from further analysis and replaced by a new one.

The sequence of Landolt Cs presented during the course of one measurement was controlled by adaptive staircase procedures (PEST; Liebermann and Pentland, 1982) with separate procedures running for the different cue conditions (valid cue versus no cue) and the different Landolt C positions (right versus left). Thus, four independent PEST strategies were implemented in one experiment, all starting with the same Landolt C gap size. Acuity thresholds for the four conditions, defined as the Landolt C gap resulting in 75% correct responses (with the chance performance level being 50%), were derived from probit analyses (McKee *et al.*, 1985) with subsequent goodness-of-fit tests which were performed on the responses obtained from at least 30 trials under each condition.

Each subject participated in three different measurements differing in the duration of the ISI (Fig. 1B) after which the Landolt C appeared in 'valid cue trials' in order to assess in more detail the time needed to shift attention. The three different ISIs tested were 100, 150 and 200 ms, resulting in stimulus onset asynchronies (SOAs) of 200, 250 and 300 ms. The sequence of measurements was randomized in each subject.

Acuity thresholds were analysed by means of three-way ANOVAs. The first one tested the acuity thresholds ($P < 0.05$) as a function of group (between), cue (within) and position (within); the second three-way ANOVA analysed the dependency of possible cueing effects (attentional benefits) on the factors group (between), interval (within) and position (within) ($P < 0.05$). Finally, in order to test whether small eye movements that could have remained unnoticed by our on-line control (fixation window of 2 or 2.25°) had an influence on the acuity thresholds, we measured the mean eye position during 'C' presentation and, thus, retinal position of the target image off-line.

Experiment 3: assessment of the size of the 'focus of spatial attention' in normal subjects

A shift of spatial attention, being imprecise in space (and/or time), will only lead to visual impairments if the degree of mislocalization is larger than the size of the visual field covered by attention, i.e. visual deficits resulting from shifts of attention being executed inaccurately will be significant if the 'focus of attention' is confined to a small area of the visual field but may be negligible if this focus is large. The purpose of experiment 3, performed with normal subjects only, was to characterize the dimensions of the visual field covered by spatial attention and, thus, to estimate the amount of dysmetria beyond which deficits in the control of covert shifts of attention could, at least in principle, be present.

As in experiment 2, covert shifts of attention were again tested by comparing peripheral acuity thresholds derived from different cue conditions. While, thus, the basic paradigm was the same as the one already described, the following experimental changes were introduced. In order to assess the size of the 'focus of attention', acuity thresholds were measured not only for a no cue and a valid cue condition but also for cue conditions in which the discriminandum appeared in the same visual hemifield but not exactly at the same location as the cue, with the relative displacement between cue and target being systematically varied. In these 'half-valid' trials, the 'C' was presented again at the fixed eccentricity of 9°, but in different angular positions relative to the fixation point as given by a displacement angle α being ±45, ±20, ±10, ±5 or ±2°. In other words, the eccentricity of

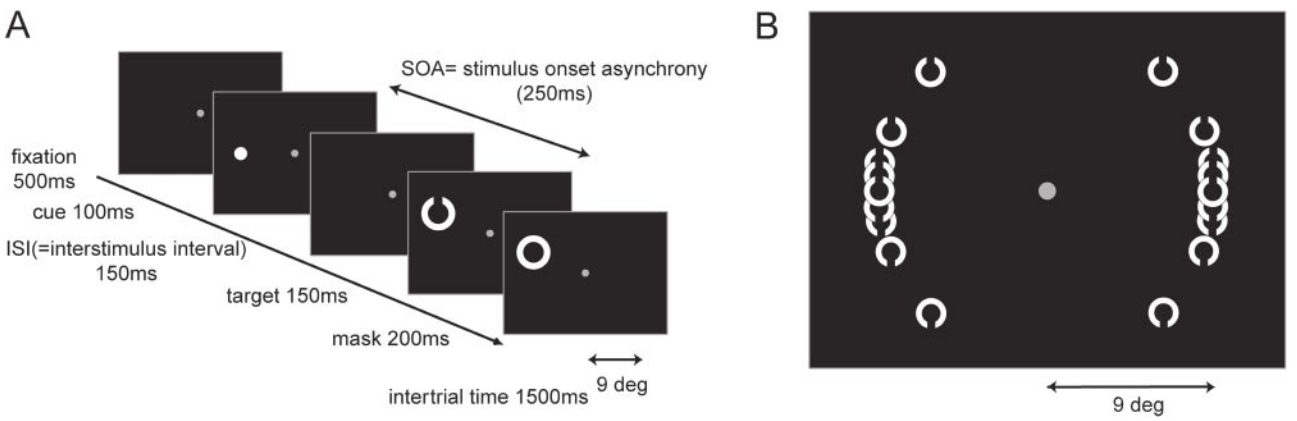

Fig. 2 Stimulus sequence of experiment 3 assessing the size of the 'focus of attention'. (**A**) Single trials started with the presentation of a central red fixation dot followed by the Landolt optotype which was announced in cue trials (shown in this example) by a white dot presented 9° right or left of the fixation point. In cue trials (96% of all trials), the following Landolt C was presented at exactly the same position as the cue ('valid cue' condition, 75% of all trials) or, alternatively, the location of the Landolt C was displaced relative to the cue, i.e. the expected location, by a given angle (±5, ±10, ±20 or ±45°; 'half-valid cue' condition). (**B**) Sketch of the 16 possible target locations in which the Landolt C could appear in 'half-valid' trials. Data collected for the same absolute displacement angles were pooled.

the target was the same (9°) but its direction relative to the (horizontal) line connecting the fixation point and the cue was varied. Unfortunately, the 2° angle displacement condition had to be discarded from the analysis due to an error in stimulus generation (confined to this single condition). Thus, the smallest displacement angle tested in fact was 5°, corresponding to the distance of the target from the cue being 0.79° of visual angle (Fig. 2B). Valid trials defined by the Landolt C appearing at the same location as the preceding cue amounted to the large majority (75%) of all trials in this experiment in order to guarantee that the cue would reliably elicit a shift of attention directed towards the cue location. In the remaining 25% of presentations, 'half-valid' and 'no cue' trials were applied, with each of the total of six conditions being presented with the same probability (4.17%). Trials with different cue and position conditions were presented pseudorandomly interleaved within one block. The sequence of Landolt Cs presented during the course of a measurement was determined by the method of constant stimuli. Within one experiment, consisting of a total of 1440 trials, the size of the Landolt C's gap was varied across six pre-defined equidistant levels ranging from 3 to 11 or, alternatively, from 3 to 13 arc min, depending on individual acuity thresholds obtained from a first acuity measurement. In order to collect sufficient data points and to allow for recreation during the long measurement, each subject underwent eight experiments separated by short breaks of a couple of minutes. Each of the eight blocks had identical parameters and consisted of 180 trials, which were finally pooled for the individual subject. The ISI was set to 150 ms in this experiment. Data collected for the same absolute displacement angles were pooled. Acuity thresholds for the valid cue, the no cue and the five half-valid cue conditions were again derived from probit analyses and subjected to a one-way ANOVA with the factor cue condition ($P < 0.05$).

Results

Experiment 1: overt shifts of spatial attention in patients with cerebellar damage and controls—comparison of visually guided saccades

Compared to the control subjects, our patients with cerebellar damage showed deficits in saccadic accuracy which were present in both horizontal directions tested. This difference between groups was reflected in both a significant increase in absolute position error of the first saccade, which averaged 1.08° in the patients compared to 0.66° in the controls (Fig. 3A; $F = 6.44$, $P = 0.018$), and a larger number of corrective saccades performed per target presentation (patients, 0.38; controls, 0.17; Fig. 3B; $F = 5.0$, $P = 0.023$). On the other hand, the two groups did not differ in the mean amplitude of the first saccade ($F < 0.001$, $P = 0.99$). The reason is that saccades of the patients were in most cases dysmetric, but individual patients differed as to their saccades being hypo- or hypermetric, resulting in a normal group mean but a larger variability of saccade amplitude (Fig. 3C, left). Figure 4 gives an example of the high variability of saccade amplitude which was observed in most of the patients. While the control subject shown in Fig. 4 is able to keep his saccade amplitude stable during the 300 trials, the saccades of the exemplary patient (Fig. 4) are grossly variable, with many of them being largely hypometric. In this patient, the saccades undershoot the target position by >2° in ~40% of all trials despite a mean absolute position error of only 1.35°.

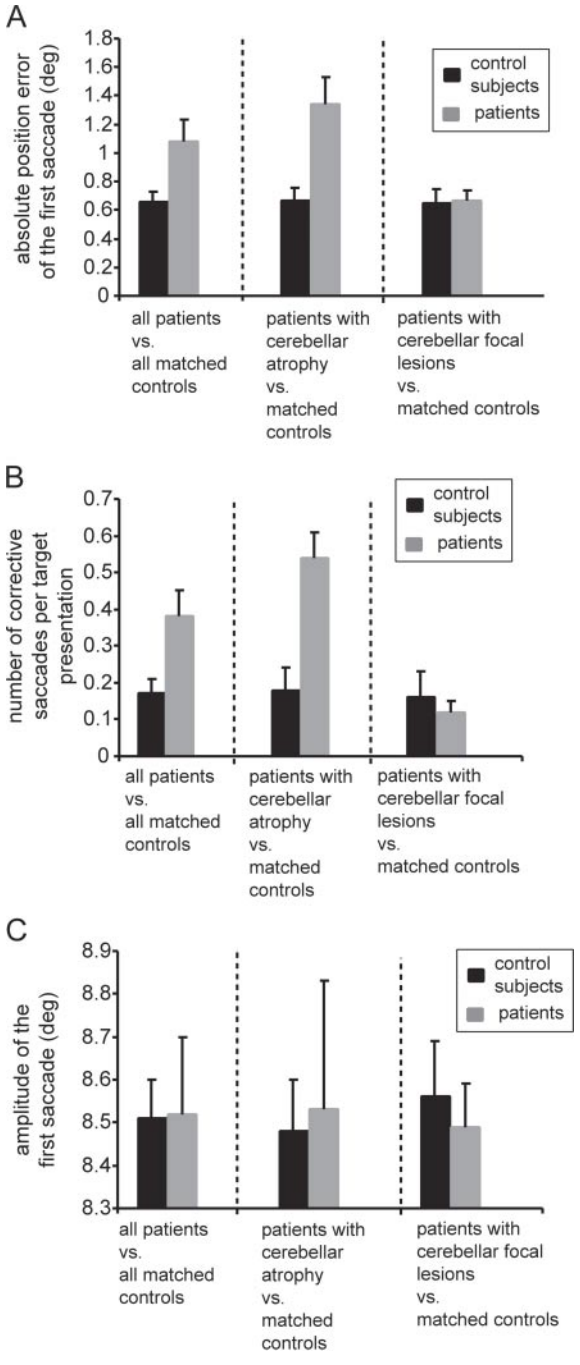

Fig. 3 Saccade performance of patients with cerebellar damage and healthy control subjects. Absolute position error of the first saccade (**A**), number of corrective saccades per target presentation (**B**) and saccade amplitude of the first saccade (**C**) for all patients compared to all age-matched control subjects (left bars) and two subgroups of patients considered (middle and right pair of bars). Error bars indicate the SEM.

When taking into account the underlying cerebellar damage, it turned out that saccade dysmetria was not present in cerebellar patients with damage sparing the cerebellar vermis.

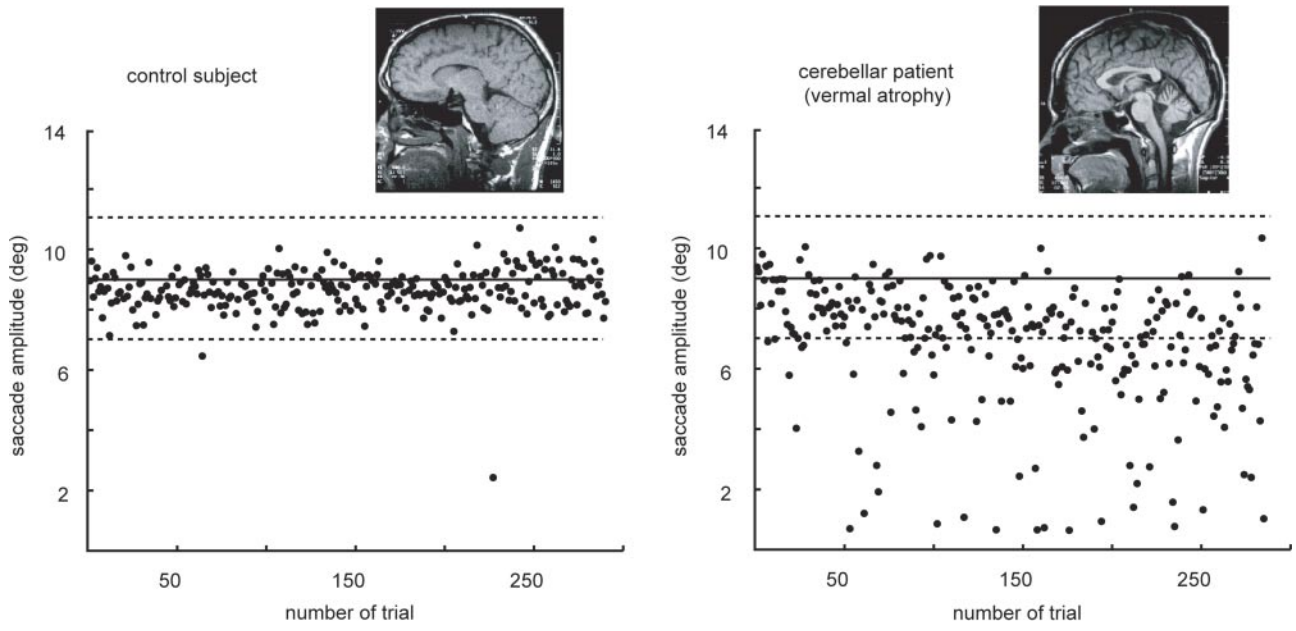

Fig. 4 Saccades performed by a control subject (left panel) and a representative patient (right panel) as a function of time. Saccade amplitude (*y*-axis) varies little for the control subject but significantly for the patient. Saccades in different directions were pooled. The middle horizontal lines indicate the true saccade target position (9°). Insets: sagittal MRI slices of the two subjects.

This conclusion is based on major differences in eye position errors and the number of corrective saccades in patients suffering from general cerebellar atrophy, including the cerebellar vermis, compared to age-matched controls, but normal performance in the second subgroup of patients with focal hemispheric lesions (Fig. 3). Specifically, patients with cerebellar damage including the vermis showed a 2-fold mean absolute position error (F = 9.56, P = 0.008) as well as a 2-fold number of corrective saccades (F = 16.01, P = 0.001) compared to the matched controls. However, as revealed by one-way ANOVAs, such significant differences were not found comparing the second patient group showing focal cerebellar damage to the matched controls (position error, F = 0.04, P = 0.85; number of corrective saccades, F = 0.344, P = 0.57). Finally, saccade latency, post-saccadic drift and the skewness of saccades were not significantly different for patients and control subjects, showing that dysmetria is the prominent feature of saccade disturbance as a consequence of cerebellar damage.

Experiment 2: comparison of covert shifts of spatial attention in patients with cerebellar damage and controls

Figure 5 reveals that both healthy controls and cerebellar patients showed improved acuity thresholds for valid cueing, i.e. when spatial information on the target position was given in advance. Specifically, the mean difference between acuity thresholds obtained from the cue condition compared to the no cue condition, averaged over all SOAs and positions, was 20% in both groups and turned out to be statistically highly significant ($P < 0.001$; Fig. 5A). It is also evident from Fig. 5 that the absolute acuity thresholds of the patients were higher than those of the healthy controls ($F = 11.57$, $P = 0.001$) and that the absolute improvement in acuity was even larger in the patients than in the controls. In order to test for differences in attentional control between groups, relative cue effects (given by the difference in acuity thresholds between conditions divided by the acuity threshold for the no cue condition) rather than absolute acuity thresholds were subjected to a two-way ANOVA with the factors group and SOA. This analysis revealed that the relative cue effects were independent not only of the group ($F = 0.22$, $P = 0.65$) but also of the SOA ($F = 0.19$, $P = 0.83$), indicating that normal subjects and patients were equally able to use spatial cues to shift their attention even within the shortest SOA tested (200 ms).

The ability to benefit from spatial cueing was spared in both subgroups of patients considered. Both patients with cerebellar atrophy and those with focal hemispheric lesions showed an improvement of visual acuity as a consequence of spatial cueing which was statistically highly significant ($P < 0.001$, each), not different from the improvement observed in the age-matched control groups ($P > 0.05$) and independent of the SOA ($P > 0.05$) (Fig. 5B and C). A significant difference in overall acuity performance observed for the total group of patients (Fig. 5A) was present only in the subgroup of patients with general cerebellar atrophy ($F = 14.9$, $P < 0.001$) but was absent in the second subgroup of patients with lesions confined to the cerebellar hemispheres ($P > 0.05$).

As mentioned in the Methods, stringent fixation criteria were applied during the measurements in order to prevent subjects from making saccades to the target position anticipated from preceding cue information. In order to rule out, furthermore, that small amplitude saccades might have been

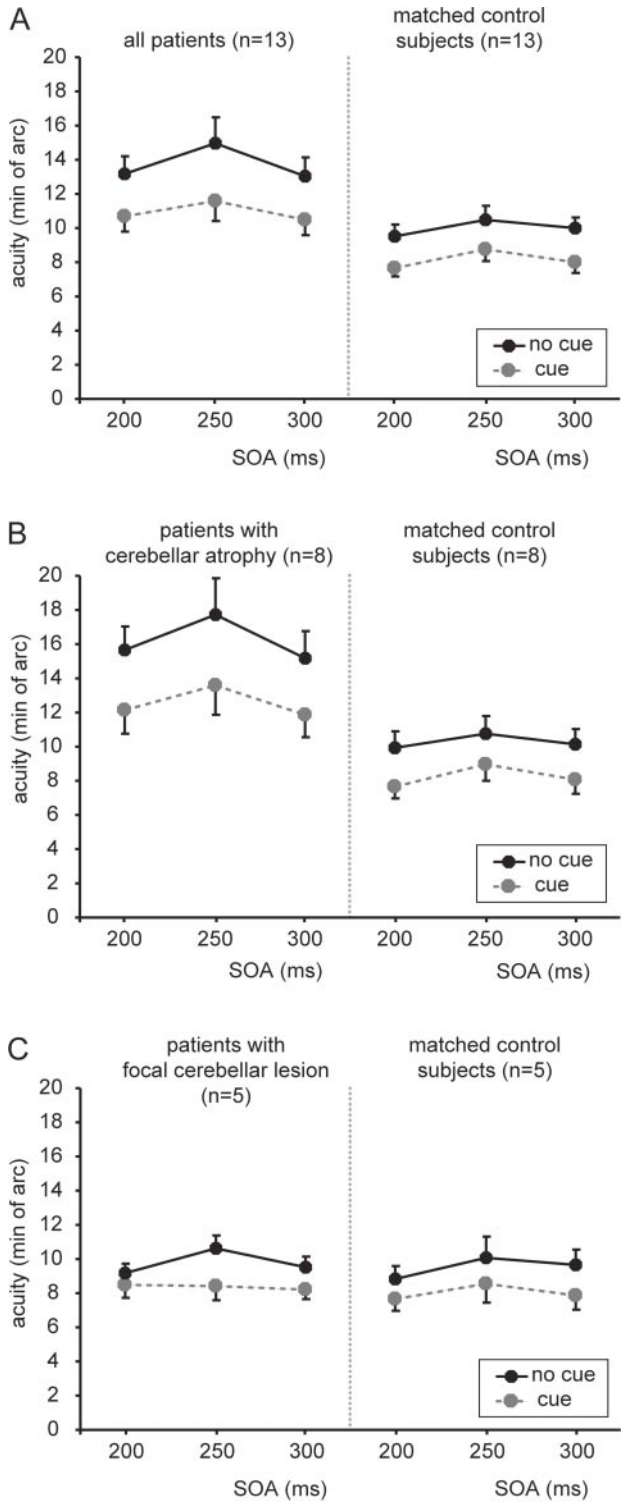

Fig. 5 Performance of the patients and of controls in the attention paradigm. Acuity thresholds under the cue and no cue condition as a function of stimulus onset asynchrony (SOA). Differences in acuity thresholds serve as an estimate of the attentional benefit induced by valid spatial cueing. Error bars indicate the SEM. Psychophysical data of all cerebellar patients (**A**; $n = 13$), of patients with cerebellar atrophy involving the vermis (**B**; $n = 8$) and of patients with focal lesions of one of the cerebellar hemispheres (**C**; $n = 5$) compared to age-matched control groups.

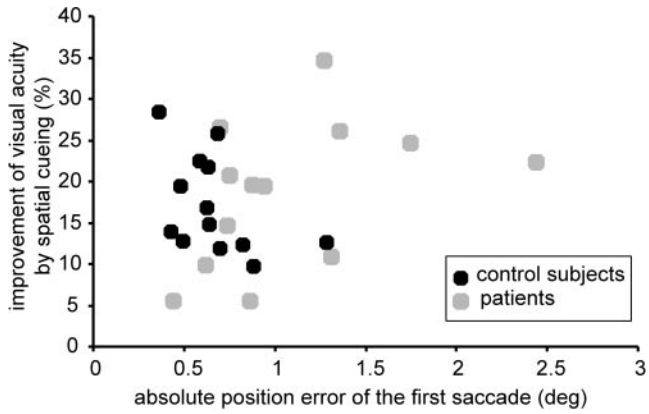

Fig. 6 Correlation between covert and overt shifts of spatial attention: improvement of visual acuity by valid spatial cueing given by the difference in acuity thresholds between conditions divided by the acuity threshold for the no cue conditions (*y*-axis) as a function of absolute position error of the first saccade (*x*-axis), i.e. the measure of saccade dysmetria, for all individual patients and control subjects.

performed in the direction of the target, unnoticed by on-line control, the quality of fixation was analysed *post hoc*. This analysis revealed that, in general, all subjects tended to fixate right of the fixation point during 'C' presentation. This bias was present in both the groups and was not significantly different for the cerebellar patients (0.22°) compared to the normal control subjects (0.58°). More importantly, the presentation of the cue induced only minor changes of eye position (<0.1° in both groups), well below the limit beyond which changes in visual acuity could be induced. Since these subtle changes in eye position were directed to the right for both cue (target) locations, they, moreover, do not provide an explanation for the symmetric improvement in visual acuity induced by spatial cueing. In summary, the analysis of eye movements did not show any differences between patients and controls that would indicate an oculomotor strategy which could have been applied by the patients in order to compensate for an attentional deficit not detected by the psychophysical results.

In a final attempt to demonstrate a cerebellar contribution to the control of spatial attention, we correlated the absolute position error, i.e. a measure of saccade accuracy, with the improvement of visual acuity by cueing. As can be seen in Fig. 6, the saccade performance of the individual subjects did not correlate with the improvement in visual acuity. This was true for both the control subjects (linear regression, $r^2 = 0.22$, $P = 0.1$) and the patients group ($r^2 = 0.19$, $P = 0.14$). Even those patients with the largest saccade errors showed a clear and strong benefit from spatial cueing in the attention paradigm.

Experiment 3: assessment of the size of the 'focus of spatial attention' in normal subjects

As in experiment 2, the subjects again showed improved acuity thresholds when the discriminandum was signalled

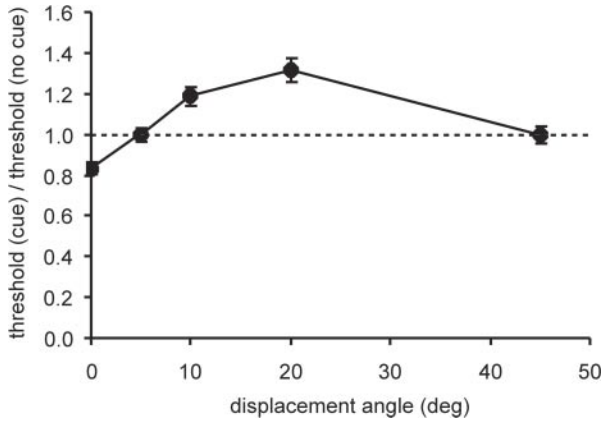

Fig. 7 The size of the 'focus of attention' is spatially restricted. Plot of a measure of attentional modulation of visual acuity as a function of the displacement angle (*x*-axis) denoting the direction in which the Landolt C was presented relative to the fixation point in cue trials (compare Fig. 2). The measure shown is given by the acuity threshold obtained for the cue condition divided by the threshold observed for the no cue condition (means and SEMs). Accordingly, values <1.0 (horizontal line) indicate improvements in acuity, whereas values >1.0 reflect a degradation in acuity compared to the no cue condition. Benefits are restricted to displacement angles <5°.

by a spatially accurate cue (Fig. 7). This improvement between thresholds (no cue versus valid cue), reflecting the perceptual consequence of spatial shifts of attention, averaged 17% in the seven normal subjects tested. In contrast to this benefit induced by valid spatial cueing, the acuity thresholds observed for 'half-valid cueing', i.e. for trials with cues indicating the correct hemifield but not the accurate location (Fig. 2B), were either qualitatively the same (displacement angle of 'C' 5 and 45°) or even higher (displacement angle of 'C' 10 and 20°) compared to the no cue condition (Fig. 7). In other words, the benefit of cueing was confined to visual displacement angles below 5°. Since a displacement angle of 5° corresponded to a distance between cue and target of 0.79° (of visual angle), we can conclude that the visual area covered by focal attention as induced in our experiment is spatially highly selective and confined to a very small area. The influence of spatial cueing on the perceptual performance with acuity thresholds improving only for spatially accurate cues was statistically highly significant as indicated by a one-way ANOVA with the factor cueing condition (no cue, valid cue, half-valid cue (four displacement angles); $F = 14.3$, $P < 0.001$) and *post hoc* comparisons (Newman–Keuls test), showing that a statistically significant improvement was present only for the valid cue condition ($P < 0.05$). Conversely, there was a significant decrease in acuity for two of the half-valid conditions compared to no cue trials (10 and 20°, $P < 0.05$; others NS). Moreover, *post hoc* comparison of the acuity thresholds observed for the valid cue condition and the half-valid cue condition revealed superior thresholds for accurate cueing ($P < 0.05$), again confirming the narrow effect of spatial shifts of attention on acuity.

Discussion

Based on neuropsychological studies of patients with cerebellar damage (Akshoomoff and Courchesne, 1992, 1994; Courchesne *et al.*, 1994*b*; Townsend *et al.*, 1996, 1999; Harris *et al.*, 1999) and functional imaging studies of healthy human subjects (e.g. Allen *et al.*, 1997), it has been suggested that the cerebellum is involved in coordinating rapid shifts of attention, similar to the way it contributes to the coordination of rapid eye movements. The goal of this study was to test directly the hypothesis that the cerebellum is involved in both overt shifts of spatial attention, i.e. saccades, and covert shifts of attention. Towards this end, we tested whether or not patients with cerebellar damage show deficits in the control of covert shifts of spatial attention mirroring the disturbances of their saccades.

As expected and in accordance with previous studies in human and non-human primates (Vilis and Hore, 1981; Noda and Fujikado, 1987; Noda *et al.*, 1988; Waespe and Baumgartner, 1992; Robinson *et al.*, 1993; Tagaki *et al.*, 1998; Barash *et al.*, 1999), our patients showed significant deficits in saccade accuracy as indicated by increased position errors and a larger number of corrective saccades compared to controls. Our analysis of the two subgroups of patients considered revealed that the deficits were present only in the one subgroup of patients showing global cerebellar atrophy including the vermis but absent in patients with lesions of the cerebellar hemispheres. This result is in line with the well established view that saccadic dysmetria is a consequence of damage to the oculomotor vermis (Tagaki *et al.*, 1998; Barash *et al.*, 1999). While absolute position errors of the first saccade were significantly increased in the patients, the mean saccade amplitude was not significantly different for the two groups (patients versus controls). This seeming paradox is due to the fact that single patients consistently showed either hypo- or hypermetric saccades. These interindividual differences in saccade amplitude presumably reflect the individual extension and location of the cerebellar damage in the single patient. Specifically, lesions of the cerebellar cortex including the oculomotor vermis have been demonstrated to result in hypometric saccades (Tagaki *et al.*, 1998; Barash *et al.*, 1999) while lesions of the fastigial nuclei—the main recipient of the projections sent out from the oculomotor vermis—lead to hypermetric saccades to the ipsilesional side and hypometric saccades to the contralesional side (Vilis and Hore, 1981; Noda *et al.*, 1988; Waespe and Baumgartner, 1992; Robinson *et al.*, 1993). Both kinds of lesions are associated with an increase in the variability of saccade amplitude (Vilis and Hore, 1981; Noda *et al.*, 1988; Waespe and Baumgartner, 1992; Robinson *et al.*, 1993; Tagaki *et al.*, 1998; Barash *et al.*, 1999), a feature also present in our patients.

In contrast to the execution of saccades, the control of covert shifts of spatial attention as assessed by measuring improvements in visual acuity prompted by spatially accurate cues was unimpaired in our patients. This conclusion can be derived from three main results. First, the relative improvement of visual acuity induced by spatial cueing was not

significantly different for patients and controls. Secondly, in both groups (patients and controls), the perceptual benefit was independent of the ISI (and the SOA), suggesting that the time needed to reallocate spatial attention was the same. Finally, there was no correlation between saccade accuracy and the performance in the attention task. Specifically, both subgroups of patients tested, i.e. the first subgroup showing saccadic dysmetria and the second one being unimpaired in the execution of saccades, were able to improve visual discrimination by the cue information in the same manner. Moreover, no significant correlation was observed when the individual saccade accuracy was correlated with the individual ability to shift attention covertly. The only significant difference between groups in the discrimination paradigm was increased acuity thresholds of the patients compared with the controls. One reason for the impaired acuity in the patients suffering from cerebellar atrophy is the possibility that their disorders might also have involved extracerebellar parts of the brain such as visual cortical areas, although MRI failed to reveal morphological lesions of cerebral cortex and clinical examination did not show any deficits other than cerebellar deficits. Alternatively, this deficit in acuity might reflect a cerebro-cortical impairment due to a loss of cerebellar efferents possibly targeting parts of visual cortex in the healthy brain. Irrespective of the specific reason, however, it is important to note that this finding does not invalidate the conclusion that the control of covert shifts of attention in the patients was intact. If some of our patients actually had subclinical lesions in extracerebellar parts of the brain, as well as in the cerebellum, then we can conclude from our results that accurate shifts of attention as induced in this study do not rely on either the cerebellum or these putative extracerebellar regions. In other words, by including patients with neurodegenerative disease, our study was highly sensitive and, if at all, prone to detect rather than to miss attention deficits.

Our conclusion is clearly at odds with the previous report of slowed covert orienting of visuospatial attention in patients with acquired cerebellar lesions (Townsend *et al.*, 1999) using a paradigm very similar to the one applied here. Specifically, Townsend *et al.* observed that patients with acquired cerebellar damage were significantly different from normal subjects. Normals could shift attention within 100 ms after cue onset—obvious by an improvement in visual performance, i.e. the discrimination of the orientation of the letter 'E', but patients needed 800–1200 ms. To explain this difference, we first of all need to know if our paradigm is sensitive enough to detect subtle disturbances in the control of spatial attention reliably. A main concern in this regard, not considered by previous work and holding also for the study of Townsend *et al.* (1999), is the possibility that attention may cover an area of the visual field that is large enough to tolerate inaccuracies in the spatial shift of attention. Experiment 3, mapping visual acuity as a function of the displacement of the discriminandum relative to the cue, provides evidence that attention is spatially restricted. Indeed, cueing led to an improvement of acuity within a small central zone flanked by a surround in which acuity was lower. Since a loss of benefit in discrimination induced by shifting attention in the wrong direction was present already for the smallest relative displacement angle tested (5°) corresponding to a distance between cue and target of 0.79°, we can conclude that the 'spotlight of attention' activated in our paradigm is highly circumscribed (diameter <1.5°) and therefore much smaller than the dysmetria evident in many of the individual saccade trials of our patients (compare Fig. 4). The estimate of the size of the 'spotlight of attention' of this study is similar to the one recently derived from monkey experiments using very much the same paradigms (Ignashchenkova *et al.*, 2004).

If we agree that the paradigm used in this study was sensitive enough to detect disturbances in the control of spatial attention, we have to consider the specific differences in experimental paradigms between this report and the study of Townsend *et al.* (1999) in order to explain the conflicting results. One possible source of the difference between our results and those of Townsend *et al.* is that the movement that our subjects made to report their perceptions, i.e. pushing a button, was simpler than the movement made by the subjects in the study of Townsend *et al.*, i.e. operating a joystick lever to indicate four possible target orientations. Ravizza and Ivry (2001) have demonstrated that some deficits of cerebellar patients in attention paradigms depend on the motor responses used. Deficits were present only when subjects made more complicated movements. This idea has received further support from a functional imaging study showing that cerebellar activation in a task involving switching attentional set reflected response reassignment rather than attentional load (Bischoff-Grethe *et al.*, 2002). A second difference is the lack of eye movement control in the Townsend study. Given the long SOAs applied (up to 1200 ms), it appears unlikely if not impossible that the subjects did not perform saccades in the direction of the cue. As a matter of fact, our subjects performed saccades in a significant number of trials for even shorter SOAs; these trials, however, were discarded from further analysis. Nevertheless, the specific pattern of results observed in the study of Townsend *et al.* seemed incompatible with the interpretation that eye movements could account for their findings. The reason is that the deficits were observed for the short SOA condition (100 ms) under which voluntary eye movements should not be elicited. However, as demonstrated here, the visual area covered by spatial attention is spatially highly restricted, leaving a cue not followed by a target at almost the same (retinal) position ineffective. It thus seems possible that involuntary eye movements such as nystagmus so common in cerebellar disease could affect attentional improvements even under short SOA conditions. Finally, the discrepant results may be due to a different emphasis placed on the analysis of the attentional effects. Specifically, a deficit in spatial attention was deduced by Townsend *et al.* from their observation that discrimination in validly cued trials was basically independent of the SOA

(100 or 1200 ms) in control subjects but better for the longer SOA compared to the shorter one in the patient groups, suggesting that orienting of attention might be slowed in the latter. This argument, however, is problematic since attention effects can be estimated reliably only by contrasting different conditions such as valid versus invalid cue conditions (Townsend study) or valid versus no cue conditions (present study). As a matter of fact, the dependency of such a differential attention measure on the SOA as asessed by the interaction between effects of group and SOA was not significant ($P < 0.06$) for the patients with acquired cerebellar lesions in the study of Townsend *et al.* (1999).

In summary, we conclude that the cerebellum is not part of a common network underlying the control of both overt and covert spatial shifts of attention. This interpretation is in line with the recent demonstration of an unimpaired performance of children with focal cerebellar lesions in a paradigm assessing the ability to focus attention and to shift attention between different modalities (Schoch *et al.*, 2004). Importantly, this conclusion by no means invalidates the general concept of non-motor functions of the cerebellum. These functions, however, are not secondary to a specific role of the cerebellum in attention because its contribution to orienting seems to be confined to the coordination of goal-directed movements such as saccades.

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