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Cognitive sequencing impairment in patients with focal or atrophic cerebellar damage

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Although cognitive impairment after cerebellar damage has been widely reported, the mechanisms of cerebro-cerebellar interactions are still a matter of debate. The cerebellum is involved in sequence detection and production in both motor and sensory domains, and sequencing has been proposed as the basic mechanism of cerebellar functioning. Furthermore, it has been suggested that knowledge of sequencing mechanisms may help to define cerebellar predictive control processes. In spite of its recognized importance, cerebellar sequencing has seldom been investigated in cognitive domains. Cognitive sequencing functions are often analysed by means of action/script elaboration. Lesion and activation studies have localized this function in frontal cortex and basal ganglia circuits. The present study is the first to report deficits in script sequencing after cerebellar damage. We employed a card-sequencing test, developed *ad hoc*, to evaluate the influence of the content to be sequenced. Stimuli consisted of sets of sentences that described actions with a precise logical and temporal sequence (Verbal Factor), sets of cartoon-like drawings that reproduced behavioural sequences (Behavioural Factor) or abstract figures (Spatial Factor). The influence of the lesion characteristics was analysed by grouping patients according to lesion-type (focal or atrophic) and lesion-side (right or left). The results indicated that patients with cerebellar damage present a cognitive sequencing impairment independently of lesion type or localization. A correlation was also shown between lesion side and characteristics of the material to be sequenced. Namely, patients with left lesions perform defectively only on script sequences based on pictorial material and patients with right lesions only on script sequences requiring verbal elaboration. The present data support the hypothesis that sequence processing is the cerebellar mode of operation also in the cognitive domain. In addition, the presence of right/left and pictorial/verbal differences is in agreement with the idea that cerebro-cerebellar interactions are organized in segregated cortico-cerebellar loops in which specificity is not related to the mode of functioning, but to the characteristics of the information processed.

Keywords: cerebellum; executive function; picture arrangement; script

Abbreviations: MRI = magnetic resonance imaging; TIQ = total intelligence quotient; WAIS-r = Wechsler Adult Intelligence Scale Revised

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Introduction

Anatomical, experimental and functional neuroimaging and clinical data stress the importance of cortico-cerebellar interactions in a variety of non-motor functions such as cognition, emotion and affective processing (Timmann and Daum, 2007). This cerebellar revolution makes a complete reconsideration of cortico-cerebellar interrelationships mandatory in order to discover the mechanisms through which the cerebellum exerts its influence on the cerebral cortex. Among the different theories on cerebellar functions (Bower and Parsons, 2003; Ito, 2006), a cerebellar role in sequencing incoming sensory patterns and outgoing responses has been proposed (Braitenberg *et al.*, 1997; Ivry, 1997; Mauk, *et al.*, 2000). Visuo-spatial implicit learning of sequences in patients with cerebellar lesions has been analysed in different experimental paradigms and cerebellar patients have been consistently reported impaired (Pascual-Leone *et al.*, 1993; Molinari *et al.*, 1997; Doyon *et al.*, 1998; Gomez-Beldarrain *et al.*, 1998). Functional magnetic resonance data in healthy subjects are controversial in discriminating the cerebellar involvement in sequence learning or in motor adaptation (Doyon *et al.*, 1998; Seidler *et al.*, 2002; Parsons *et al.*, 2005).

Conversely, neurophysiological studies in healthy volunteers or in patients with focal cerebellar damage indicated a role of the cerebellum in sequence acquisition/detection (Molinari *et al.*, 1997; Restuccia *et al.*, 2007).

Acquiring and acting upon a serial order of events is a fundamental ability that can lead to sequence structure knowledge either incidentally through experience (implicit learning) or intentionally through explicit effort (declarative learning). To recognize that stimuli are presented in a given order, the sensory information pertaining to one stimulus must be kept active in a working memory system and compared with subsequent stimuli. Procedural learning can be achieved only if the correct sequence of events (sensory or motor) is acquired implicitly or explicitly. Thus, a disruption of 'sequence in' processing of stimuli could be responsible for the implicit learning impairment.

The severity of cerebellar patients' difficulty in the serial reaction time task in detecting a visuo-spatial sequence, indicates a prevalent role of cerebellar circuitry in recognizing event sequences, rather than in planning and executing them (Molinari *et al.*, 1997). Tesche and Karhu (2000), with a somatosensory evoked paradigm, analysed the neural signal generated in the cortex and in the cerebellum during the presentation of somatosensory sequences perturbed by random stimulus omissions. While the response in the somatosensory cortex was closely linked to the actual presentation of the stimulus, cerebellar activity was particularly evident when the expected stimulus was omitted (Tesche and Karhu, 2000). As stated by Ivry (2000), this finding provides experimental evidence of a cerebellar role 'as detector of change or deviation in the sequence of sensory events'.

To verify whether cerebellar processing affects the ability to recognize the similarity/diversity of incoming sequence inputs, the somatosensory mismatch negativity (S-MMN) component of event-related potentials (ERPs) was recently analysed in six patients with unilateral cerebellar lesions (Restuccia *et al.*, 2007). In all subjects analysed, MMN was clearly abnormal in the cerebral hemisphere contralateral to the cerebellar damage. This evidence identifies the cerebellum as the ideal structure for detecting discordances between the input from the deviant event and the sensory memory representation of the regular aspects of sequence stimulation.

Support for a cerebellar role in the acquisition of procedural sequences also derives from animal data. In a series of studies based on surgical lesions it was shown that cerebellar damage impairs the acquisition of the spatial procedural sequences required for Morris water maze test in rats (Petrosini *et al.*, 1998). The good performances of animals, that have acquired the correct competence before the lesion, underline the specificity of the cerebellum in acquisition rather than execution (Leggio *et al.*, 1999). Furthermore, evidence that the cerebellar lesioned rats were impaired not only in learning through direct execution but also in learning through observation of conspecific behaviour, provides additional proof of the importance of the cerebellum in sensory processing (Leggio *et al.*, 2000*a*; Graziano *et al.*, 2002).

Thus, detecting and generating sequences might be a key for understanding the basic cerebellar function in different domains. If so, the ability to detect and generate sequences should represent an operational mode also in the cognitive domain. To investigate this topic (Experiment 1) we first retrospectively investigated the performances of patients with cerebellar lesions on the Picture Arrangement subtest (PAs) of the Italian version of the Wechsler Adult Intelligence Scale Revised (WAIS-r) (Orsini and Laicardi, 1997); and second (Experiment 2) we analysed whether the characteristics of the material processed influenced sequence detection performances of cerebellar-damaged subjects.

Experiment 1—WAIS-r Picture Arrangement subtest

The PAs of the WAIS-r mainly investigates sequential thinking. To solve the task correctly visual material has to be analysed, understood and integrated (Lezak, 1995). The correct logical sequence is reconstructed by identifying relations between events, deciding priority and ordering these events in chronological order (Orsini and Laicardi, 1997). In Experiment 1, PAs subtest performances of patients affected by pathologies exclusively confined to the cerebellar structures, who were admitted to the IRCCS Santa Lucia Foundation rehabilitation hospital between 2003 and 2006, were retrospectively reviewed.

Subjects

Based on lesion lateralization and focal or degenerative aetiology, 77 right-handed patients, i.e. 44 males and 33 females were divided into the following groups: patients affected by focal cerebellar lesions on the right side (Table 1: RCb—n.21); patients affected by focal cerebellar lesions on the left side (Table 1: LCb—n.21); and patients affected by cerebellar atrophy. These latter patients were grouped either considering all subjects independently from aetiologies (CA—n.35 Experiment 1 Supplementary Material Table 1) or considering only subjects with idiopathic cerebellar ataxia (Table 1: ICA—n.18). Therefore according to the grouping methods the total number of cerebellar subjects was 77 (Cbt group Experiment 1 Supplementary Material Table 1) or 60 (Cb group Table 1).

Focal cerebellar lesions consisted of ischemic or haemorrhagic stroke or surgical ablation due to arteriovenous malformations or tumours. Lesion characteristics were reconstructed from the written reports of the charts. No clinical or radiological evidence of extracerebellar pathologies were reported, with the exception of one subject that presented an involvement of the brainstem. One subject

Table 1 Experiment 1: Demographic, motor and cognitive data

Group	No	M/F	Age	Education	Motor score[a]	TIQ WAIS-R
Cb	60	36/24	48.93 (17.04)	10.68 (4.27)	9.07 (5.33)	96.45 (14.56)
RCb	21	15/6	53.29 (18.44)	10.71 (4.55)	8.19 (5.54)	100.71 (14.47)
LCb	21	12/9	49.76 (17.98)	11.19 (4.32)	7.48 (6.75)	97.57 (9.88)
ICA	18	9/9	42.88 (12.81)	10.05 (4.04)	12.06 (4.74)	90.17 (17.58)
C	69	23/46	43.78 (15.96)	11.39 (4.07)	–	106.17 (12.45)

Mean values and standard deviations.
Cb = patients affected by cerebellar pathologies considered as a whole group; RCb = patients affected by focal cerebellar lesions on the right side; LCb = patients affected by focal cerebellar lesions on the left side; ICA = patients affected by idiopathic cerebellar ataxia; C = control subjects; TIQ = total intelligence quotient. Standard deviation in brackets.
[a]0–42 cerebellar motor score modified from (Appollonio *et al.*, 1993): higher score indicates higher motor impairment.

had a temporary, moderate, increase of the volume of the ventricles not requiring surgical derivation and not associated with comatose conditions.

Of the patients with cerebellar atrophy 12 had a genetically determined diagnosis (2: ataxia-oculomotor apraxia type 2, 5: Friedreich ataxia, 2: spino-cerebellar ataxia type 2, and 3: spino-cerebellar ataxia type 1), 1 presented atrophy as sequaele of a cerebellitis and 22 presented idiopathic forms. Of the idiopathic forms, 17 subjects presented pure cerebellar syndromes, four subjects presented additional extracerebellar atrophy (3: brainstem atrophy and 1: bilateral posterior parietal atrophy), one subject presented spastic paraparesis beside cerebellar deficits. The diagnosis of ICA was based on clinical indications of a purely cerebellar syndrome and on magnetic resonance imaging (MRI) evidence of atrophic pathology restricted to the cerebellum.

Differences in the grouping of atrophic subjects might influence the results; therefore we run statistics following both grouping methods. Since no differences were evidenced, in the results section only data from the more selective series of patients with ICA will be presented. Data on the statistical comparisons considering the entire group of subjects with degenerative pathologies (CA) are reported in Supplementary Material (Filename: Experiment 1—Test with CA group).

Some of these patients had already participated in previous studies (Leggio *et al.*, 2000*b*; Molinari *et al.*, 2004, 2005; Restuccia *et al.*, 2007). All patients underwent a neurological examination and their motor impairment was quantified using a modified version of the cerebellar motor deficit scale, proposed by Appollonio *et al.* (1993), which ranges from 0 (absence of any deficit) to 42 (presence of all deficits to the highest degree) and evaluates eight cerebellar signs (dysarthria, limb tone, postural tremor, upper and lower limb ataxia, standing balance, gait ataxia and ocular movements). See Table 1 for group characteristics. The control group consisted of 69 subjects who had no history of neurological or psychiatric illness (Table 1: C—n.69). Mean age and education of control subjects is reported in Table 1. *t*-Test for independent samples confirmed that cerebellar patients and control subjects were well-matched for age (P = n.s.) and education (P = n.s.). Furthermore a one-way ANOVA failed to reveal any differences in age [$F(3,125) = 2.59$, P = n.s.] or years of education [$F(3,125) = 0.58$, P = n.s.] among C group and cerebellar subgroups. Experimental procedures were approved by the ethical committee of the IRCCS Santa Lucia Foundation; written consent for anonymous use of clinical data was obtained from each subject.

Neuropsychological assessment

The patients' general cognitive profile was assessed from data available on their charts. In particular, we considered the following data: WAIS-r total intelligence quotient (TIQ) values, immediate and delayed recall of Rey's 15 words (Rey, 1958), immediate visual memory (Carlesimo *et al.*, 1996), forward and backward digit span and forward and backward Corsi Test (Corsi, 1972), Raven's 47 progressive matrices (Raven, 1949), freehand copying of drawings (Gainotti *et al.*, 1977), copying drawings with landmarks (Gainotti *et al.*, 1977), temporal rules induction (Villa *et al.*, 1990) and word fluency (Borkowsky *et al.*, 1967). The same Italian version of the WAIS-r reported in the charts was employed to test control subjects.

The picture arrangement subtest of the WAIS-r

The PAs consists of 10 sets of cartoon pictures that tell stories. Each set, comprised of three to six pictures, is presented to the subject in scrambled order with instructions to rearrange the pictures to make the most sensible story. The PAs was administered and scored according to the Italian version of the WAIS-r (Wechsler, 1981; Orsini and Laicardi, 1997, 2003).

Statistical analysis

Student's *t*-test for independent samples was used to detect differences between cerebellar patients and control subjects. Metric units were compared by one-way ANOVA. When significant differences were found, post-hoc comparisons

Table 2 Experiment 1: Neuropsychological assessment

Group	IR	DR	IVM	PM	WF	CD	CDL	FDS	BDS	FC	BC	TRI
Cb	40.15 (8.84)	8.37 (2.76)	19.30 (2.16)	26.57 (5.73)	28.84 (12.02)	8.84 (1.72)	66.80 (6.03)	5.76 (1.01)	3.93 (1.10)	4.88 (0.90)	4.42 (1.30)	10.76 (7.06)
RCb	37.98 (9.88)	8.24 (3.08)	19.57 (2.11)	28.07 (3.63)	27.33 (15.07)	9.27 (1.57)	67.54 (3.04)	5.52 (0.93)	4.00 (1.22)	4.75 (0.85)	4.48 (1.40)	11.07 (7.21)
LCb	41.74 (8.31)	8.61 (2.76)	19.27 (2.60)	27.11 (5.05)	33.99 (11.34)	9.01 (2.05)	65.71 (9.67)	6.15 (0.81)	4.10 (1.02)	5.00 (0.89)	4.52 (1.47)	9.18 (5.74)
ICA	40.69 (8.28)	8.23 (2.53)	18.99 (1.89)	24.43 (7.59)	25.15 (5.83)	7.96 (1.24)	67.07 (3.08)	5.61 (1.20)	3.67 (1.03)	4.88 (0.99)	4.24 (0.97)	12.16 (8.21)
CUT OFF[a]	*28.53*	*4.69*	*13.85*	*18.93*	*17.35*	*7.18*	*61.85*	*5.00*	*3.00*	*5.00*	*3.00*	*15.00*

Mean data and standard deviations.
IR = Rey's 15 mots short term (immediate recall); DR = Rey's 15 mots long term (delayed recall); IVM = immediate visual memory; PM = Raven's 47 (progressive matrices); WF = word fluency; CD = copying drawings; CDL = copying drawings with landmarks; FDS = forward digit span; BDS = Backward digit span; FC = forward Corsi; BC = backward Corsi; TRI = temporal rules induction; group abbreviations as in Table 1. Standard deviation in brackets.
[a]Pathological values are inferior to cut off levels in all tests with the exception of TRI in which pathological values are superior to cut off level.

among groups were assessed with the Bonferroni *post hoc* test; Bonferroni adjusted *P*-values (P_{Bonf}) are reported. Pearson correlations among motor scores and PAs scores were calculate to verify possible relations between motor performances and cognitive performances.

Results

Cerebellar patients showed no obvious deficits in the general neuropsychological assessment. The TIQ values of cerebellar patients and control subjects (Table 1) as well as the scores of the neuropsychological assessment of cerebellar patients (Table 2) were within the normal range except for the forward Corsi test, which was just above the cut-off. TIQ scores were employed to compare cognitive levels among groups; significant differences were present among the control subjects and the three subgroups of cerebellar patients [One-way ANOVA: $F(3,125) = 7.89$, $P = 0.001$]; Bonferroni *post hoc* comparisons showed that ICA group had scores significantly lower than controls ($P_{Bonf} = 0.000$).

Regarding the PAs, all experimental groups scored within the normal range (10 ± 3) (Wechsler, 1981; Orsini and Laicardi, 1997, 2003). However, all cerebellar group scores were lower than C group scores (Fig. 1). An independent samples *t*-test demonstrated that the difference between the performances of Cb and C groups was significant ($P < 0.001$). This finding was further confirmed by a multiple comparison among the three subgroups of cerebellar patients and the C group [One-way Anova: $F(3,125) = 10.97$, $P < 0.001$]. *Post hoc* analyses (Bonferroni Test) demonstrated that all patient subgroups performed worse than control subjects (RCb: $P_{Bonf} = 0.011$; LCb: $P_{Bonf} = 0.002$; ICA: $P_{Bonf} = 0.000$), while no difference was detected between subgroups of cerebellar patients. Pearson correlation results did not highlight any relation between ataxia and PAs scores (Table 3).

Cerebellar subjects as a group and considering type and side of lesion presented a preserved general cognitive pattern. The lack of deficits of clinical relevance is not

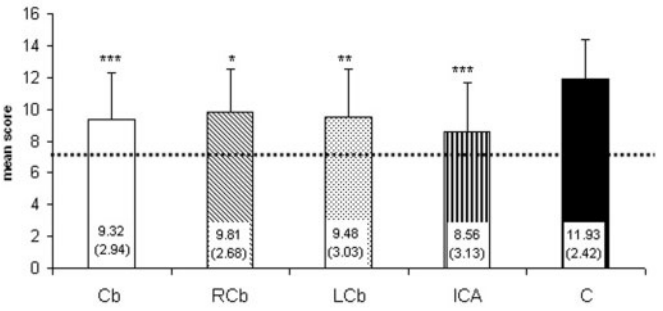

Fig. 1 Experiment 1. Picture Arrangement subtest mean data and standard deviations. Dashed line indicates cut-off value. Abbreviations as in Table 1. Statistical significance versus C group: $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.001$.

Table 3 Experiment 1: Pearson Correlation

Ataxia score		PAs
Total ataxia	Pearson correlation	0.142
	Significance (two-tailed)	0.279
Upperlimb	Pearson correlation	−0.167
	Significance (two-tailed)	0.203
Ocular	Pearson correlation	−0.047
	Significance (two-tailed)	0.720
Dysarthria	Pearson correlation	−0.088
	Significance (two-tailed)	0.505

completely surprising. In different domains such as language, working memory and visuo-spatial abilities, just to name a few, cerebellar deficits have been evidenced only in ad hoc testing conditions (Silveri *et al.*, 1998; Leggio *et al.*, 2000*b*; Molinari *et al.*, 2004; Justus, 2004; Restuccia *et al.*, 2007). Although on the PAs cerebellar patients' performances were within the normal range, they were clearly defective when compared to control group performances. As stated in the 'Introduction' section, different lines of reasoning prompted us to hypothesize a sequencing deficit after cerebellar damage.

Experiment 2

In order to solve the PAs of the WAIS-r correctly, various aspects of the material to be sequenced have to be taken into account at the same time. To analyse whether cerebellar influences on sequential processing are material related, we tested cerebellar patients with new, specifically developed sets of cartoon-like drawings/texts.

Subjects

Forty-five right-handed patients (25 males and 20 females) with cerebellar lesions were recruited from those admitted to the IRCCS Santa Lucia Foundation rehabilitation hospital. Some of these subjects were already included in Experiment 1 since they had previous admissions to the hospital. According to the focal or diffuse localization of the cerebellar damage, the total group of patients was divided into subgroups: subjects with right cerebellar lesions (RCb: n.11), subjects with left cerebellar lesions (LCb: n.9) and subjects affected by cerebellar atrophy. These latter patients were grouped either considering all subjects independently from aetiologies (CA—n.25 Experiment 2 Supplementary Material Table 1) or considering only subjects with idiopathic cerebellar ataxia (ICA—n.14). Therefore according to the grouping methods the total number of cerebellar subjects was 45 (Cbt group Experiment 2 Supplementary Material Table 1) or 34 (Cb group Table 1).

All subjects with focal lesions did not present any clinical or radiological evidence of extracerebellar involvement or increased intracranial pressure at the time of testing. Three subjects had positive history of moderate increase of the volume of the ventricles in the very acute phase. None of them received surgical derivation or intracranial pressure direct measurement. In all cases, the ventricular dilatation was not accompanied by comatose conditions and was resolved in few days. Lesion characteristics of RCb and LCb groups according to the MRI images are described in Table 4 and in Fig. 2. Table 4 reports vascular and gross anatomical subdivisions touched by the lesion, while Fig. 2 depicts two selected coronal sections involving the core of the lesion.

Of the patients with cerebellar atrophy 1 presented atrophy as sequaele of a cerebellitis, 1 had a paraneoplastic atrophy, 11 had a genetically determined diagnosis (2: ataxia-oculomotor apraxia type 2, 6; Friedreich ataxia, 2: spino-cerebellar ataxia type 2, and 1: spino-cerebellar ataxia type 1), and 12 presented idiopathic forms. Of the idiopathic forms, seven subjects presented pure cerebellar syndromes and five, beside cerebellar deficits, presented additional extracerebellar signs (three peripheral neuropathy, one spastic paraparesis and one spastic paraparesis and convergence insufficiency). The diagnosis of ICA was based on clinical indications of a purely cerebellar syndrome and on MRI evidence of atrophic pathology restricted to the cerebellum. As in Experiment 1, differences in the grouping of atrophic subjects, considering CA or ICA groups, might influence the results; therefore we run statistics following both grouping methods.

Table 4 Experiment 2: lesion characteristics in subjects with focal cerebellar lesions

Case Code	Side	Lesion	PICA	AICA	SCA	DCN	ANT	POST	Hem	Vermis
Cb1	R	ischemic			x		x			x
Cb2	L	ischemic	x					x	x	
Cb3	L	ischemic	x		x			x	x	
Cb4	R	surgical				x		x		x
Cb5	R	surgical					x			x
Cb6	R	surgical						x	x	
Cb7	R	ischemic			X				x	
Cb8	L	surgical				x	x	x	x	x
Cb9	R	ischemic	x		x	x		x	x	x
Cb10	R	hemorrhagic				x		x	x	x
Cb11	R	hemorrhagic				x		x	x	
Cb12	L	surgical						x	x	
Cb13	L	ischemic		x	x	x	x	x	x	x
Cb14	R	surgical				x		x	x	x
Cb15	R	ischemic			x	x	x	x	x	x
Cb16	L	hemorrhagic				x			x	x
Cb17	L	hemorrhagic				x		x	x	
Cb18	L	ischemic	x			x				
Cb19	R	ischemic	x					x	x	
Cb20	R	surgical						x	x	

PICA = postero inferior cerebellar artery; AICA = antero inferior cerebellar artery; SCA = superior cerebellar artery; DCN = deep cerebelar nuclei; ANT = anterior cerebellar lobe; POST = posterior cerebellar lobe; Hem = cerebellar hemisphere; R = right; L = Left.

Since no differences were evidenced, in the results section only data from the more selective series of patients with ICA will be presented. Data on the statistical comparisons considering the entire group of subjects with degenerative pathologies (CA) are reported in Supplementary Material (Filename: Experiment 2—Test with CA group).

The patients' motor impairment was quantified using the same motor scale employed in Experiment 1 (Appollonio *et al.*, 1993). See Table 5 for patients' characteristics. A random sample of 132 healthy subjects, matched for age and education with the cerebellar group and with no history of neurological disease, comprised the control group (C group). Mean age and education of control subjects is reported in Table 5. An independent samples *t*-test confirmed that the C group was well-matched with the Cb group for age (P = n.s.) and years of education (P = n.s.). Furthermore, a one-way ANOVA among the C group and the subgroups of cerebellar patients failed to reveal any differences in age [$F(3,159) = 1.85$, P = n.s.] or years of education [$F(3,159) = 1.47$, P = n.s.).

Experimental procedures were approved by the ethical committee of the IRCCS Santa Lucia Foundation; written consent was obtained from each subject according to the Declaration of Helsinki.

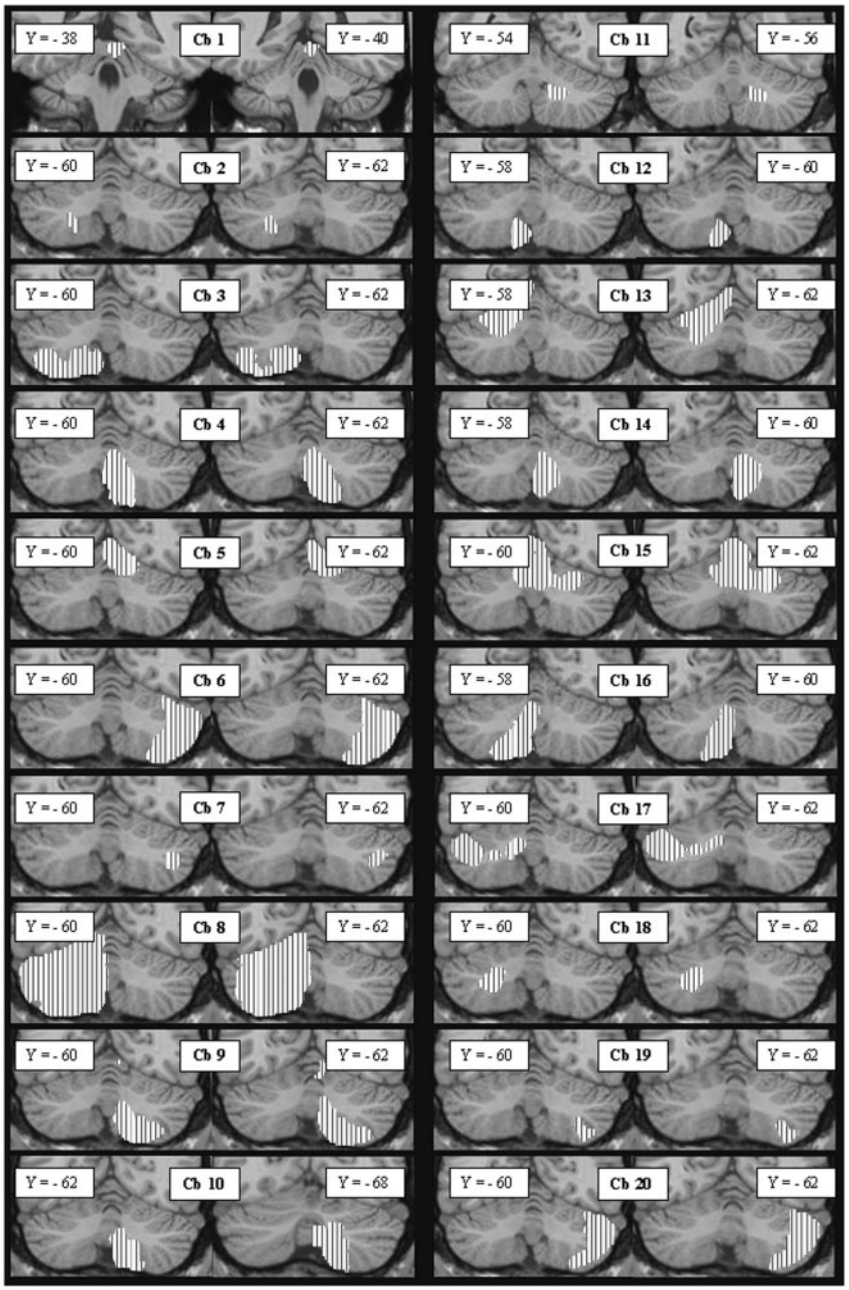

Fig. 2 Experiment 2. Subjects with focal lesions: lesion extent in two representative coronal sections for each individual. Lesion is presented as overlaid on coronal T1-weighted template from (Schmahmann *et al*., 2000). Lesion extensions were assessed on the 3D-T1-MPRAGEs after spatial normalization. Case codes as in Table 4.

Table 5 Experiment 2: Demographic, motor and cognitive data

Group	No	M/F	AGE	Education	Motor score[a]	Raven's 47
Cb	34	18/16	51.94 (14.77)	11.32 (4.41)	10.38 (7.32)	27.05 (6.32)
RCb	11	6/5	48.18 (20.72)	13.73 (4.41)	7.89 (7.14)	28.50 (3.52)
LCb	9	2/7	60.63 (7.42)	10.75 (4.20)	7.66 (6.80)	29.60 (3.56)
ICA	14	5/9	49.36 (11.08)	10.00 (4.14)	14.37 (6.85)	24.74 (8.23)
C	132	57/75	47.02 (17.33)	12.80 (4.41)	–	29.50 (2.52)

Mean values and standard deviations.
Abbreviations as in table 1. Standard deviation in brackets.
[a]0–42 cerebellar motor score modified from (Appollonio *et al.*, 1993).

Methods

The same battery described in Experiment 1 was used to assess the general cognitive profile of the cerebellar patients in Experiment 2 (Table 6). In the present experiment, a test specifically developed to differentiate content-related effects on sequential information processing was administered. The test consisted of 16 sets of cards; each set was comprised of six cartoon-like drawings or six sentences to be ordered in a logical sequence. The cartoon-like drawings depicted behavioural sequences or abstract figures. The former were correctly sequenced by taking into account time and semantic and spatial coding; the latter were ordered exclusively according to spatial cues. The sentences had to be ordered to form logically consistent short narratives. Out of the 16 sets of cards, 4 reconstructed abstract figures, 4 short narratives, 8 reproduced behavioural sequences; of these last sets, 4 were based on human figurines and 4 on object disposition.

Scoring was based on entirely correct sequences and correct fragments. Calculation was performed using the 'Ratio of repetition' (RR) proposed by Cofer (1966). Thus, two cartoon-like drawings in correct succession were considered the shortest fragment of a sequence to be evaluated. Each correct fragment was computed independently of its right or wrong position in the whole sequence (for instance, if the correct answer was 1 2 3 4 5 6 and the subject's answer was: 2 3 4 6 1 5, the sequence 2 3 4 represented a correct fragment). The RR was obtained using the following formula:

$$RR = \frac{(\text{Correctly sequenced cards}) - (\text{Correct sequence fragments})}{\text{Total number of cards} - 1}$$

Thus, RR values run from zero to one. The task was administered without a time limit.

Data from the 132 healthy subjects were pre-processed for item analysis. This analysis excluded 5 out of the 16 sets of cards. To analyse whether the performances on the remaining 11 sets clustered, a factor analysis was performed. Analysis of the principal component, with extraction of the three factors and an oblique rotation of the axis, was carried out. Since the intercorrelation among factors resulted lower than 0.18, confirming the hypothesis of the independence among factors, we executed an analysis of the principal component with an orthogonal rotation of the axis (Varimax). The factorial saturation of the rotated solution is reported in Table 7.

Thus, 11 out of the 16 sequences clustered around three factors. All four sentence sequences, three out of the four abstract sequences and four out of the eight behavioural sequences clustered. Thus, only these clustering sequences were considered for further analyses. The full set of used stimuli is available as Supplementary Material (Figs 1–3).

The three factors that resulted from the factor analysis were indicated as:

- VERBAL FACTOR (Ve) script sequences n. 4. (Fig. 3A).
- SPATIAL FACTOR (Sp) abstract sequences n. 3. (Fig. 3B).
- BEHAVIOURAL FACTOR (Be) behavioural sequences n. 4. (Fig. 3C).

To detail the relations between verbal versus non-verbal factors we calculated verbal/behavioural (Ve/Be) and verbal/spatial (Ve/Sp) indexes for each subject. These indexes were calculated by subtracting the Sp mean score from the Ve mean score and the Be mean score from the Ve mean score, respectively.

Table 6 Experiment 2: Neuropsychological assessment

Group	IR	DR	IVM	PM	WF	CD	CDL	FDS	BDS	FC	BC	TRI	TQI
Cb	43.37 (7.07)	9.14 (2.38)	19.47 (1.99)	27.05 (6.32)	27.93 (12.57)	8.36 (2.18)	65.01 (7.62)	5.59 (1.13)	3.91 (1.38)	4.97 (1.00)	4.68 (0.98)	9.08 (7.33)	96.18 (15.93)
RCb	44.33 (7.24)	9.37 (2.50)	19.28 (1.95)	28.50 (3.52)	30.81 (17.77)	9.15 (1.37)	67.13 (2.70)	5.82 (0.60)	4.36 (1.12)	4.91 (0.83)	4.64 (1.12)	12.59 (11.01)	99.6 (16.5)
LCb	43.33 (7.87)	8.95 (3.25)	20.46 (1.30)	29.60 (3.56)	29.28 (3.52)	9.19 (2.10)	62.73 (13.07)	5.78 (0.67)	4.11 (1.17)	5.11 (1.36)	5.22 (0.97)	6.28 (3.22)	103.8 (9.3)
ICA	42.74 (6.84)	9.07 (1.52)	18.98 (2.27)	24.74 (8.23)	22.78 (6.83)	7.16 (2.35)	64.77 (5.54)	5.29 (1.59)	3.43 (1.60)	4.93 (0.92)	4.36 (0.74)	7.86 (3.11)	89.21 (17.36)
CUT	*28.53*	*4.69*	*13.85*	*18.93*	*17.35*	*7.18*	*61.85*	*5.00*	*3.00*	*5.00*	*3.00*	*15.00*	*70.00*
OFF[a]													

Means and standard deviations.
Abbreviations as in tables 1 and 2. Standard deviation in brackets.
[a]Pathological values are inferior to cut off levels in all tests with the exception of TRI in which pathological values are superior to cut off level.

In this analysis, positive values indicate better performances in the verbal factor.

Statistical analysis

Student's *t*-test for independent samples was used to detect differences between the two groups. To identify among-group differences metric units of the results of each group were compared by one-way ANOVA. When significant differences were found, *post hoc* comparisons among groups were assessed with the Bonferroni *post hoc* test; Bonferroni adjusted *P*-values (P_{Bonf}) are reported. To assess whether the patients exhibited significantly different performances in the three factors a repeated measures ANOVA was performed (within-subjects factor: Ve, Sp, Be; between-subjects factor: group).

Pearson correlations among motor scores and sequencing factors scores were calculated to verify possible relations between motor performances and sequence results.

Results

As in Experiment 1, in this experiment cerebellar patients did not present any clear deficits in the general neuropsychological assessment except in the forward Corsi test (Table 6).

Raven's 47 progressive matrices (PM) results were employed (Raven, 1949) to compare cognitive levels among groups (Table 5). An independent samples *t*-test demonstrated a significant difference between C and Cb groups ($P<0.001$). Significant differences were also present among the control subjects and the three subgroups of cerebellar patients [one-way ANOVA: $F(3,159)=12.36$; $P<0.001$]. However, Bonferroni *post hoc* comparisons showed that ICA group had scores significantly lower than each other groups (versus C group: $P_{Bonf}=0.000$; versus RCb: $P_{Bonf}=0.001$; versus LCb: $P_{Bonf}=0.000$).

The Cb group's RR scores were clearly lower than those of the C group on all tasks (Fig. 4). Independent samples *t*-test demonstrated these significant differences (Ve: $P<0.001$; Sp: $P<0.001$; Be: $P<0.001$). Moreover, when cerebellar patients' performances were considered taking into account type and side of damage, performances of all groups on all tasks were lower than those of controls (Fig. 4). The ICA group's performances were very similar on Ve and Be tasks; conversely, LCb and RCb performances varied according to the factor considered with a specular profile. LCb patients had low Be scores and better Ve performances. On the contrary, RCb patients presented low Ve scores and better Be performances (Fig. 4). One-way Anovas showed significant differences among groups for each task [Ve: $F(3,159)=11.56$; $P<0.001$; Sp: $F(3,159)=7.77$; $P<0.001$; Be: $F(3,159)=8.02$; $P<0.001$]. Bonferroni *post hoc* test confirmed lesion-side differences. The RCb group scored significantly lower than the C group on the Ve factor ($P_{Bonf}=0.002$), while the LCb group scored significantly lower than the C group on the Be ($P_{Bonf}=0.013$) and Sp factors ($P_{Bonf}=0.019$). The ICA group's scores were significantly lower than the C group's scores on all factors (Ve Factor: $P_{Bonf}=0.000$; Be Factor: $P_{Bonf}=0.001$; Sp Factor: $P_{Bonf}=0.006$). A repeated measures Anova confirmed the differences among groups [between-subjects effect: $F(3,159)=2191.185$; $P<0.001$] and also

Table 7 Experiment 2: Factorial saturation of the rotated solution

	Be	Ve	Sp
Be 1	**0.69**	0.22	−0.18
Be 2	**0.66**	0.29	0.20
Be 3	**0.54**	0.21	0.33
Be 4	**0.69**	−0.23	0.06
Ve 1	0.07	**0.58**	0.07
Ve 2	−0.16	**0.77**	0.03
Ve 3	0.35	**0.50**	0.01
Ve 4	0.27	**0.44**	0.25
Sp 1	0.14	0.08	**0.69**
Sp 2	−0.32	0.24	**0.66**
Sp 3	0.42	−0.12	**0.54**

Ve = verbal Factor; Be = behavioral factor; Sp = spatial factor.

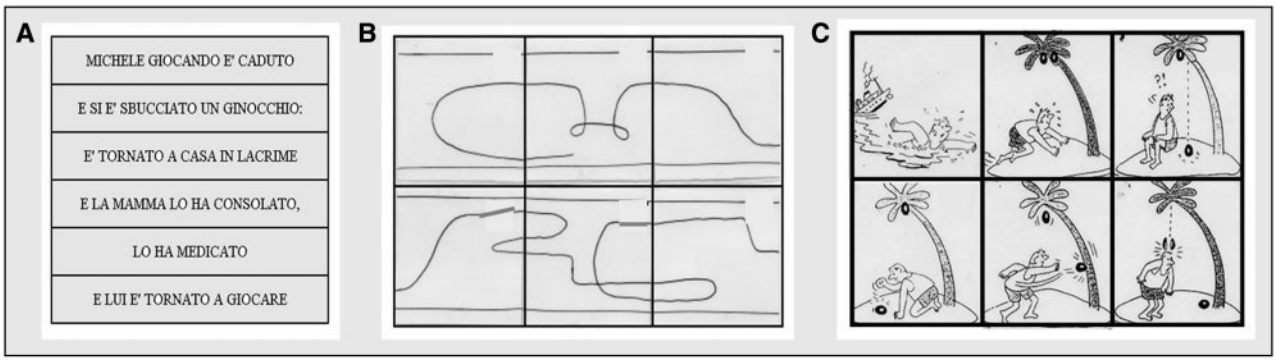

Fig. 3 Experiment 2. Set of cards representative of the three factors. (**A**) Verbal factor. Michel fell while playing/and he bruised his knee:/he went back home crying/and his mother comforted him,/she medicated him/and he went back to play. (**B**) Spatial factor. (**C**) Behavioural factor.

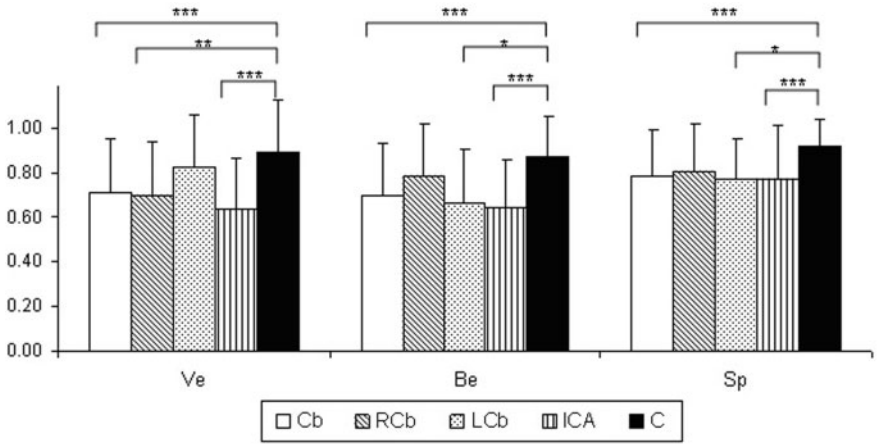

Fig. 4 Experiment 2. Histograms of mean RR scores in patient and control groups. Ve = verbal factor; Be = behavioural factor; Sp = spatial factor; group abbreviation as in Table 1. $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.001$.

Table 8 Experiment 2: Pearson correlation

Ataxia score		Be	Ve	Sp
Total ataxia	Pearson correlation	−0.420*	−0.423*	0.224
	Significance (two-tailed)	0.019	0.018	0.225
Upperlimb	Pearson correlation	−0.299	−0.375*	0.221
	Significance (two-tailed)	0.102	0.038	0.232
Ocular	Pearson correlation	−0.258	−0.303	0.101
	Significance (two-tailed)	0.162	0.097	0.587
Dysarthria	Pearson correlation	−0.474**	−0.405*	0.189
	Significance (two-tailed)	0.007	0.024	0.308

*Significant at the 0.05 level (two-tailed); **significant at the 0.01 level (two-tailed).

highlighted that groups presented factor dependent performances [within-subjects effect: $F(2,318) = 4.35$; $P < 0.05$].

Pearson correlation results highlighted relations between ataxia and sequencing (Table 8). Ocular subscore did not correlate with performances in any of the three sequencing factors. Total cerebellar deficit score and dysarthria subscore significantly correlated with the performances in Be and Ve factors while upper limb subscore significantly correlated with the performances in Ve factor.

Further investigation of the relations between lesion side and content to be sequenced was made by analysing the verbal/behavioural (Ve/Be) and verbal/spatial (Ve/Sp) indexes (Fig. 5). According to these analyses, especially for the Ve–Be data, all non-lateralized groups (C, Cb, CA) tended toward a balance in the two parameters with values around 0. Conversely, in the two groups with lateralized lesions a clear prevalence was present with positive values in the LCb group and negative values in the RCb group. The one-way ANOVA revealed significant differences for both Ve/Be index [$F(3,159) = 2.67$, $P < 0.05$] and Ve/Sp index [$F(3,159) = 2.68$, $P < 0.05$]. Bonferroni *post hoc* test reveals that the only significant difference was between RCb and LCb patients (Ve/Be index: $P_{Bonf} = 0.035$; Ve/Sp index: $P_{Bonf} = 0.035$).

Discussion

The present data indicate that subjects affected by cerebellar pathologies are impaired on card-sequencing tests in which scrambled cards have to be arranged in a logical order independently from the material processed. Impairment was present in the PAs of the WAIS-r as well as in the different tasks of Experiment 2, regardless of the nature of the cerebellar lesion (atrophic or focal) and the lesion side (right or left).

Picture Arrangement, as analysed by the WAIS, has been considered to evaluate the capacity to process behavioural sequences and different terms, such as action script or semantic sequencing, have been used more or less indifferently to refer to such a function. In the present study, we referred to script sequencing as the process that allows recognizing correct spatial and temporal relations among behaviourally relevant actions. Script sequencing has been considered to be sustained by frontal lobe and basal ganglia circuits (Tinaz *et al.*, 2006). Regardless of whether script-sequencing presentation is verbal or pictorial, deficits have been reported in subjects with frontal cortex (Sirigu *et al.*, 1998; Zanini *et al.*, 2002) or basal ganglia lesions (Zalla *et al.*, 1998; Tinaz *et al.*, 2008). Although the cerebellum has been considered to be highly involved in sequence processing (Braitenberg *et al.*, 1997) and sequencing deficits in processing sensory and motor information are widely reported in subjects with cerebellar damage (Molinari *et al.*, 1997; Timmann *et al.*, 2004), the cerebellar role in script sequencing has never been addressed. One aspect of sequencing functions often highlighted is the ability to plan ahead and order meaningful events chronologically (Tinaz *et al.*, 2006). Neurophysiological data in healthy subjects (Tesche and Karhu, 2000), lesion

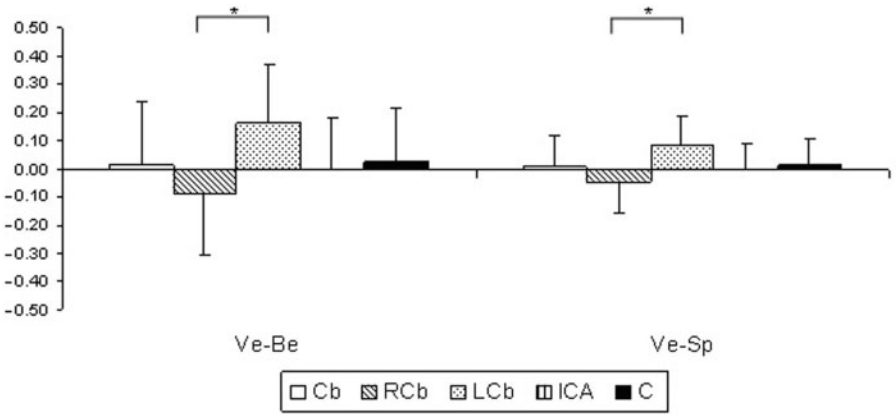

Fig. 5 Experiment 2. Histograms of Ve–Be and Ve–Sp mean indexes in patient and control groups. Ve–Be = Verbal minus Behavioural scores, Ve–Sp = Verbal minus Spatial scores; group abbreviations as in Table 1. $^{*}P < 0.05$.

studies after cerebellar damage (Restuccia *et al.*, 2007) and experimental evidence of focal lesions in animal models (Nixon, 2003) all point to the cerebellum as the key structure for preparing responses to predictable sensory events. Card-sequencing tasks require examining visual or verbal material in order to understand spatial, temporal and/or semantic relationships and correctly reconstructing the strings in logical sequences. In other words, subjects have to extract elements that will allow predicting the next card in the sequence out of the complex array of sensory information. Patients with cerebellar damage were able to rearrange only small fragments of whole strings. This deficit was not related to deficits at the level of perception since, when requested to analyse cartoon-like drawings individually, they were extremely competent in verbally describing the content.

As regards to possible influences of the motor ataxia impairment on the sequence performances it must be said that no time limit was applied and no fine movement was associated with the cart-sorting responses. Thus, motor impairment *per se* cannot be considered a determinant factor of the lower sequencing score of the cerebellar patients. Nevertheless, correlations were found between behavioural and verbal factors and motor ataxia and dysarthria scores, as well as between verbal factor and upper limb score (Table 8). This evidence might support interesting speculations on the importance of impaired sequencing for motor and cognitive functions (Ackermann *et al.*, 2004).

Furthermore, general cognitive deterioration cannot explain the specificity of the script sequencing deficits observed. All groups of cerebellar patients presented normal IQ values (Experiment 1) and their scores on Raven's 47 progressive matrices were within the cut-off (Experiment 2). In a direct comparison with the control group, ICA subjects presented significantly lower values than controls. Nevertheless, ICA scores were still within the normal range (Table 5). In detail IQ values of ICA subjects were sparse with different subjects in the pathological range.

Finally, defects in elementary perceptual or verbal analyses are not a conceivable explanation. Cerebellar patients were able to solve correctly the visuo-spatial and verbal tasks of the WAIS-r and the BDM battery that clearly cannot be solved in the presence of significant defects in perceptual or verbal analysis.

These findings constitute the first report of a script sequencing impairment after cerebellar damage.

Timmann and colleagues (Timmann *et al.*, 2004; Frings *et al.*, 2004, 2006) analysed the ability of patients with cerebellar dysfunction to acquire sequence information from sensory inputs of different modalities and found conflicting results. These authors related discrepancies in their findings regarding differences in the motor characteristics of the different tasks employed and hypothesized that the cerebellar role in sensory sequence learning 'may become evident only if the sequence information has to be connected with a significant motor response' (Frings *et al.*, 2006).

Richter *et al.* (2004) tested subjects affected by degenerative cerebellar disease using different experimental paradigms of visuomotor associative learning. In one condition, they had to learn to associate one colour with a motor response. In another condition, they had to learn to associate two colours with a motor response. In both the conditions motor response was a right or a left key press. Cerebellar patients learned considerably less in the stimulus–stimulus-response condition than in the stimulus-response condition. Furthermore, when the sequence of colours was the reverse of that in the previous and following blocks, only the control subjects showed an increase in reaction time, suggesting that cerebellar patients did not use the sequence information to reduce reaction time across tasks (Richter *et al.*, 2004). Thus, also in this case the key aspect is the impaired processing of sequence information present in cerebellar patients. Support for the hypothesis of a cerebellar role in processing script sequence information derives from an fMRI study that demonstrated increased activity in the right dentate nucleus correlating to sequence length and complexity but not to motor parameters (Boecker *et al.*, 2002). Deficits in processing

sequential information have also been reported in different experimental models in rats. Gaytan-Tocaven and Olvera-Cortes reported that bilateral lesions of the dentate nucleus impair the acquisition of a 'new' sequential egocentric-based task (Gaytan-Tocaven and Olvera-Cortes, 2004); in a series of studies, Petrosini and co-workers demonstrated deficits in the acquisition of sequential procedures after hemicerebellectomy (Petrosini *et al.*, 1998; Leggio *et al.*, 1999, 2000*a*).

Shin and Ivry (2003) investigated the role of the cerebellum and the basal ganglia in learning spatial and temporal sequences and in integrating them when they were simultaneously present. Unlike Parkinson's disease patients, who were unable to learn the relationship between the two sequences but acquired the spatial and temporal sequences individually, cerebellar patients failed to show any evidence of sequence detection and acquisition, indicating that the cerebellum plays a central role in sequence learning in general (Shin and Ivry, 2003).

In the present work we specifically analysed the performances of cerebellar patients in script sequencing and in sequencing non-behaviourally relevant abstract figures. Script sequencing requires using both spatial and temporal information while abstract figure sequencing can rely exclusively on spatial information. Subjects with cerebellar lesions were impaired in both conditions. These data indicate that cerebellar processing is required in both script and spatial sequencing and, together with previous data on cerebellar sequencing functions, support the hypothesis of a central role of cerebellar circuits in sequence processing regardless of whether the material processed is sensory (Bower, 1997), motor (Thach *et al.*, 1992) or behavioural (present work).

Within this general framework supporting the widespread influence of the cerebellum on sequencing, indications of a more selective role emerged from the present data on patients with unilateral cerebellar damage. Statistical evaluation of performances on the different card-sequencing tasks demonstrated significant differences between subjects with right and left focal lesions. Indeed, patients with lesions of the left hemicerebellum performed defectively on script sequences based on pictorial material. Conversely, patients with lesions of the right hemicerebellum were impaired, exclusively on script sequences requiring verbal elaboration. The relation between right cerebellar hemisphere and verbal processing appears stronger than the relation between left hemisphere and non-verbal processing. Specificity of the cortico-cerebellar interactions or differences in the two patient groups' characteristics might explain the observed variability. These data not only demonstrate that the cerebellum has a specific role in elaborating sequential information pertaining to cognitive domains, but also that the ability to integrate different information in correct logical sequences is linked to the specific characteristic of the material to be processed. Thus, sequencing in general requires cerebellar processing and different cerebro-cerebellar circuits might be engaged depending on the material to be sequenced. This hypothesis is in agreement with the existence of a crossed cerebello-cortical loop organized in segregated channels that reach specific cortical zones (Schmahmann and Pandya, 1997; Middleton and Strick, 2000; Giannetti and Molinari, 2002). Different authors have stressed that this precise topography could represent the hardware that allows the cerebellum to intervene in many functions pertaining to motor control as well as to cognition (Molinari *et al.*, 2002; Schmahmann, 2004; Ito, 2005, 2006).

Supplementary material

Supplementary material is available at *Brain* online.

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