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Patients with focal cerebellar lesions show reduced auditory cortex activation during silent reading

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ABSTRACT

Functional neuroimaging studies consistently report language-related cerebellar activations, but evidence from the clinical literature is less conclusive. Here, we attempt to bridge this gap by testing the effect of focal cerebellar lesions on cerebral activations in a reading task previously shown to involve distinct cerebellar regions. Patients ($N = 10$) had lesions primarily affecting medial cerebellum, overlapping cerebellar regions activated during the presentation of random word sequences, but distinct from activations related to semantic prediction generation and prediction error processing. In line with this pattern of activation–lesion overlap, patients did not differ from matched healthy controls ($N = 10$) in predictability-related activations. However, whereas controls showed increased activation in bilateral auditory cortex and parietal operculum when silently reading familiar words relative to viewing letter strings, this effect was absent in the patients. Our results highlight the need for careful lesion mapping and suggest possible roles for the cerebellum in visual-to-auditory mapping and/or inner speech.

1. Introduction

A large body of functional neuroimaging studies has shown cerebellar activations in a range of linguistic tasks (Fedorenko, Behr, & Kanwisher, 2011; Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010; Keren-Happuch, Chen, Ho, & Desmond, 2014; Stoodley & Schmahmann, 2009; Xu, Kemeny, Park, Frattali, & Braun, 2005). In contrast, the evidence of cerebellar involvement in language from the clinical literature is more equivocal (Mariën et al., 2014). Subtle language deficits have been reported in cerebellar patients, including dysarthric speech (Urban, 2013), problems discriminating between phonemes based on temporal cues (Ackermann, Gräber, Hertrich, & Daum, 1997), reduced verbal working memory capacity (Kirschen et al., 2008), mild agrammatism (Mariën et al., 2014) and problems with aspects of higher-level language function (Murdoch, 2010). However, profound persistent language deficits are uncommon following cerebellar pathology (Alexander, Gillingham, Schweizer, & Stuss, 2012). Moreover, the functional mapping of the linguistic cerebellum clearly lags behind the corresponding mapping of the linguistic cerebral cortex (Price, 2010, 2012). Given that the integration of lesion mapping and imaging studies has proven fruitful in increasing our understanding of specific language functions of the cerebral cortex (Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013; Jefferies, 2013), a similar strategy has the promise to shed light on how the cerebellum contributes to language function.

It has been suggested that the cerebellum – in language processing as in motor control – encodes internal models that transform information about the current contextual state (sensorimotor or linguistic) to predictions about the next state (Argyropoulos, 2011; Argyropoulos, Kimiskidis, & Papagiannopoulos, 2011; Argyropoulos & Muggleton, 2013; Ito, 2008; Lesage, Morgan, Olson, Meyer, & Miall, 2012). Consistent with this hypothesis, in a recent fMRI study using healthy young controls, the BOLD response in lateral posterior cerebellum to the final word of a sentence was stronger when the sentence established a strong semantic expectancy, compared to when the final word was not predictable (Moberget, Gullesen, Andersson, Ivry, & Endestad, 2014). Especially pronounced activations were observed when the final word violated the semantic prediction, consistent with the hypothesis of error-based learning in the cerebellum (Doya, 1999; Ito, 2006; Ramnani, 2006). In addition to the predictability effects in lateral

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cerebellum, an experimental contrast comparing contextually isolated single words to perceptually matched, but meaningless, consonant strings revealed activations in more medial cerebellar regions, presumably related to more general (non-predictive) aspects of language processing. All cerebellar activations were observed in tandem with distributed cortical activation patterns, suggesting integrated cerebro-cerebellar functional networks (Buckner, 2013; Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011) for language processing (Fedorenko et al., 2010, 2011).

In the present study, we examine the impact of focal cerebellar lesions on task-related activations in the cerebral cortex. A priori, one might expect the cerebellar pathology to produce either hypo- or hyperactivations relative to controls; respectively suggesting either a failure to recruit cerebral network nodes (Baillieux et al., 2010; Mariën, De Smet, Paquier, & Verhoeven, 2010) or compensatory re-organization of function (Hattori et al., 2009; Nudo, 2013; Thiel et al., 2001). Importantly, we hypothesized that the spatial overlap between the cerebellar pathology in the patients and activation patterns in our previous fMRI study would predict the specific experimental conditions revealing significant group differences in cortical activation.

2. Materials and methods

2.1. Participants

12 patients (6 female, 6 male) who had undergone surgical resections of cerebellar pilocytic astrocytomas (primarily in childhood and adolescence) were recruited from the Department of Neurosurgery and the Department of Psychosomatic Medicine at Oslo University Hospital. Two female patients were excluded from the analysis, one due to having received additional radiation treatment and one due to technical problems during scanning. Of the remaining 10 patients (see Table 1 for demographic information), one was left-handed, perhaps due to his right hemisphere cerebellar lesion. Importantly, this patient had left-lateralized language function, as evidenced by the fMRI-activations.

Mean age at surgery was 9 years (SD: 9.1; range 3–34), while mean time since surgery at the time of testing was 12.2 years (SD: 5.3; range: 2–20). Two patients had been treated for post-surgical hydrocephalus with shunt-implants. One patient met the diagnostic criteria for several ICD-10 psychiatric diagnoses within the domains of mood and anxiety disorders (Sheehan et al., 1998).

10 age-matched healthy control participants (see Table 1 for demographic information) were recruited from the local community. The data for nine of these participants were included in our original report (Moberget et al., 2014). Control participants were self-reported as right-handed and reported no neurological or current psychiatric problems. All participants had normal or corrected-to-normal vision and were native Norwegian speakers.

Table 1
Group demographic characteristics.

Measure	Patients ($N = 10$)	Controls ($N = 10$)	Effect size[a]	p-value[b]
Sex (n female)	4	6	.200	.371
Age (years)	21.2 (6.9)	21.8 (6.3)	.010	.842
Handedness (n right)	9	10	.229	.305
Education (years)	11.3 (1.8)	13.4 (2.8)	.940	.060

[a] For categorical variables, we give Fisher's *Phi*, while for continuous variables Cohen's d is used.

[b] P-values are based on chi-square tests for categorical variables and on independent samples t-tests (two-tailed) for continuous variables. Ps < .05 are marked in bold.

The study was approved by the Regional Ethics Committee of Southern Norway (REK-Sør), and written informed consent was acquired from all participants. For participants younger than 18, written informed consent was also acquired from a parent.

2.2. Cognitive testing

All participants completed a battery of neuropsychological tests lasting approximately one and a half hour. The Vocabulary and Matrix Reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (WASI) were used to assess general cognitive abilities (Wechsler, 1999). In addition, we tested psychomotor speed (Color Naming and Reading parts of the Color-Word Interference Test from the D-KEFS battery (Delis, Kaplan, & Kramer, 2001)), working memory (Digit Span and Letter Number Span, from WAIS-III; (Wechsler, 1997)), executive function (Inhibition and Inhibition/Switching parts of the Color Word Interference Test Color-Word Interference Test from the D-KEFS), Verbal Fluency (from D-KEFS), and verbal (California Verbal Learning Test – II, (Delis, Kramer, Kaplan, & Ober, 2000)) and visuospatial (Brief Visuospatial Memory Test – Revised (Benedict, 1997)) learning and memory. With the exception of estimated IQ (calculated according to the WASI manual), we report raw test scores. All statistical analyses of neuropsychological test scores were conducted using IBM SPSS Statistics Version 21. For IQ, group differences were examined with independent samples t-test (since IQ scores are corrected for sex and age). All other test scores were examined using analyses of covariance (ANCOVAs), with sex and group as fixed factors and age as a covariate.

2.3. Experimental paradigm

The experiment was identical to that used in our previous study (Moberget et al., 2014), and the trial structure is illustrated in Fig. 1. Briefly, on each trial, the participant viewed a fixation cross, followed by a visual prompt (asterisk) and a sequence of five centrally presented words (in lower case). Each of these stimuli was presented for 750 ms, and there was no pause between successive stimuli (0 ms inter-stimulus interval). We used a fixed rate of stimulus presentation to minimize the disruptive effects of serial reading, while placing minimal demands on working memory.

Our crucial experimental variable, the predictability of the terminal, target word, was manipulated by varying the context established by the initial four words. In the *Congruent* condition, sentences were constructed so that the target word was highly predictable (e.g., "two plus two is *four*."). In the *Incongruent* condition, the sentences were also designed such that the target word was highly predictable, but this prediction was violated by presenting a terminal word that was inappropriate given the context (e.g. "[the water] had frozen to *cars*"). In the *Scrambled* condition, the initial four words did not establish a context for a grammatical sentence (e.g. "fast in clock plane"), and thus the target word was not predictable (e.g. "*through*"). We also included a *Letter String* condition to control for the visual and motor aspects of the task, replacing the words with meaningless letter strings of identical consonants (e.g. "rrr gggg nnnn pp kkkk").

Immediately after the presentation of the target word (or consonant string), the question, "Was the sentence meaningful?" was presented on the screen, indicating that the participant should judge whether or not the sequence constituted a meaningful sentence (*Congruent* condition vs. *Incongruent*, *Scrambled* & *Letter String* conditions). This question was displayed for 3000 ms and the participant was required to respond within this time window by pressing one of two buttons with his/her right hand, using the index finger ("yes") or thumb ("no"). Participants were instructed to wait for the question before answering, and were told that there

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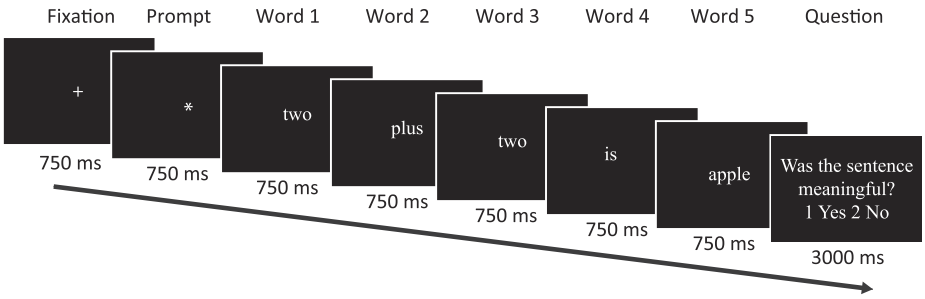

Fig. 1. Schematic of the trial structure for a trial in the incongruent condition.

was no need to respond quickly. The behavioral task was included to ensure that participants paid attention to the stimuli and was not intended as a crucial experimental measure. The onset of the next trial followed directly after the offset of the question.

The entire experiment consisted of 30 trials per condition, plus 15 null trials in which an asterisk replaced the words/letters for the full trial duration. The order of the 135 trials was randomized. Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) and MR-compatible goggles with two LCD-displays (VisualSystems®, NordicNeuroLab, Bergen, Norway), while responses were collected using an MR-compatible response grip with two response buttons (ResponseGrip®, NordicNeuroLab, Bergen, Norway). The total duration of the single functional scanning run was approximately 19 min.

The sentences were constructed with the aim of maximizing the predictability of the final word in the congruent and incongruent conditions, with the additional constraint that the target words in the incongruent condition constitute a violation of these predictions. We confirmed this by presenting 100 participants with the context phrase (four initial words) for the 30 congruent and 30 incongruent sentences and asking them to generate a terminal, target word. Cloze probability, the ratio of participants who used the actual target word to complete the sentences, was 0.85 (SD: 0.19) for congruent sentences and 0 for incongruent sentences.

Word frequency, defined as the number of occurrences per million words, was extracted from a large database of Norwegian words (The Text Laboratory, ILN, University of Oslo. http://www.tekstlab.uio.no/frekvensordlister/). As discussed in Moberget et al. (2014), the stimulus sets were not perfectly balanced across conditions in terms of word frequency for the terminal word. However, as control analyses in our previous study revealed only minimal effects of word frequency, we conducted the analyses with the full dataset. Moreover, while there were significant differences in mean RT between conditions, this factor had minimal effect on the main contrasts of interest. Based on these findings, and the absence of any significant RT differences between patients and controls in the current sample (see Section 3), we opted to not include RT-measures as additional covariates in the present analyses.

2.4. Image acquisition

Scanning was conducted on a 3 Tesla, Phillips Achieva whole body scanner, with an 8 channel Philips SENSE head coil (Philips Medical Systems, Best, the Netherlands). Functional images were obtained with a single-shot $T2^*$ weighted echo planar imaging (EPI) sequence (repetition time (TR): 2000 ms; slice echo time (TE): 30 ms; field of view (FOV): 240 × 240 × 108; imaging matrix: 80 × 80; flip angle 80° 36 axial slices, interleaved at 3 mm thickness, no gap, voxel size 3 × 3 × 3 mm). The scanning session consisted of 563 volumes, synchronized to the onset of the experiment. To obtain complete coverage of the cerebellum, the slice orientation was adjusted to be approximately 45° relative to the line running from the anterior to posterior commissure. This orientation resulted in parts of the posterior frontal lobe and superior parietal lobe falling outside the field of view. A T1 weighted anatomical image with a voxel size of 1 × 1 × 1 mm was recorded for registration of the functional images (180 sagittal slices; TR: 8.5 ms; TE: 2.3 ms; FOV: 256 × 256 × 180; flip angle: 7°).

2.5. Lesion reconstruction

For each patient, lesions were manually drawn on the T1-weighted volume using MRICron (Rorden, Karnath, & Bonilha, 2007). FLAIR volumes were used to correct the T1-based lesion maps when the former indicated more extensive tissue damage. An experienced neurologist reviewed all lesion maps. We subsequently used the SUIT-toolbox (Diedrichsen, 2006) in SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8), to normalize all lesion maps into common space and extract information about affected cerebellar lobules and nuclei using the probabilistic cerebellar atlas in SUIT. Finally, we used the normalized lesion maps to compute maps displaying lesion overlap in MRIcron (Rorden et al., 2007).

2.6. Functional image analysis

Functional images were converted to four-dimensional NIfTI files (http://lcni.uoregon.edu/~jolinda/MRIConvert/) and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Functional images were corrected for slice timing, realigned to correct for residual head movement, and co-registered to the anatomical image. Anatomical images were normalized to the MNI template using the unified segmentation and normalization algorithm implemented in SPM8 (Ashburner & Friston, 2005), and the resulting transformation parameters were then applied to the functional images. Functional images were smoothed with a Gaussian kernel of 8 mm FWHM and analyzed using a general linear model (GLM). Event-related regressors, modeled as delta functions time-locked to the onset of the target word, were created for the four trial types (congruent, incongruent, scrambled, letter strings). These functions were convolved with the canonical hemodynamic response function. Low frequency drifts were removed using a high-pass filter (cutoff 128 s) and 6 head motion parameters from the realignment step were included as additional regressors. Serial correlations in fMRI time series were accounted for by the autoregressive AR(1) model. Contrast images from the individual level analyses were included in a second level GLM with Group (controls, patients) as the binomial regressor.

A significance level of 5% (FDR corrected for multiple comparisons) was adopted for all analyses. To this end, we set a voxel-wise cluster-forming threshold of $p < .005$ (uncorrected), with sta-

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tistical significance assessed by evaluating the volume of the active clusters (Chumbley & Friston, 2009). Unthresholded statistical maps were uploaded to the NeuroVault.org database and are available at http://neurovault.org/collections/160/. Anatomical location of significant activation clusters was determined using the Anatomy toolbox for SPM (Eickhoff, Heim, Zilles, & Amunts, 2006; Eickhoff et al., 2007; Eickhoff et al., 2005).

3. Results

3.1. Cognitive function

Table 2 summarizes estimated IQ and the neuropsychological test results for the patients and controls.

Compared to age-matched controls, the patients with cerebellar lesions showed reduced performance on tests measuring general cognitive function (estimated IQ), verbal working memory, verbal fluency and verbal learning and memory, with medium to large effect sizes (Cohen, 1992). Note that while IQ by definition has a population mean of 100 and a standard deviation of 15 (Wechsler, 1999), the mean IQ in our sample of healthy controls is higher. However, a recent study (Zeller et al., 2013) testing a large (N = 130) and representative (62% of all eligible patients) Norwegian sample of young (mean age: 28.4) acute lymphoblastic leukemia survivors report similar values for WASI estimated IQ (mean: 114.0, SD: 9.41) as the healthy controls in the current study.

3.2. Lesion reconstruction and overlap with cerebellar task-related activations

Fig. 2 gives an overview of (a) affected lobules and nuclei in individual patients; (b) lesion overlap for the group; and (c) the spatial correlations between the lesion overlap map and cerebellar activations seen in our previous study of healthy young adults (Moberget et al., 2014). Cerebellar lesions primarily affected midline structures, including the vermis, paravermal hemispheric areas and the deep cerebellar nuclei (Fig. 2a). The mean volume of cerebellar resections was 20.7 cm^3 (SD: 13.7), ranging from 6.14 cm^3 to 43.36 cm^3. Of the deep cerebellar nuclei, the fastigial nuclei were the most affected (mean percentage lesioned: left: 62%; right: 70%), followed by the interposed nuclei (left: 57%; right: 62%), with the dentate nuclei being the least affected (left: 23%; right: 24%).

Table 2
Estimated IQ and raw scores on neuropsychological measures.

Measure	Patients (N = 10)	Controls (N = 10)	Effect size[a]	p-value[b]
Estimated IQ (WASI)	95.5 (7.9)	112.7 (8.2)	2.25	**.000**
Digit span	13.3 (3.1)	16.9 (3.4)	1.17	**.040**
Letter-number sequencing	9.1 (2.2)	11.7 (2.2)	1.27	**.019**
CWIT – naming	34.0 (8.0)	28.8 (3.4)	.81	.115
CWIT – reading	25.5 (10.2)	20.6 (2.4)	.58	.247
CWIT – inhibition	66.3 (29.7)	52.0 (13.5)	.54	.283
CWIT – Inhibition/switching	74.6 (25.7)	57.0 (6.5)	.93	.069
Word fluency – phonetic FAS	31.6 (8.5)	47.4 (10.8)	1.75	**.005**
Word fluency – categories	42.5 (9.1)	46.6 (8.7)	.28	.338
Word fluency – switching	14.0 (2.5)	15.8 (2.8)	.60	.233
CVLT – learning	51.5 (8.0)	61.5 (6.6)	1.73	**.003**
CVLT – delayed recall	11.8 (2.6)	13.9 (2.0)	1.53	**.006**
BVMT – learning	25.2 (4.4)	29.0 (5.5)	.91	.079
BVMT – delayed recall	10.1 (1.4)	10.9 (2.2)	.63	.213

[a] Cohen's d.
[b] P-value and effect size for full-scale IQ is based on independent samples t-test (two-tailed). For all other measures, p-values and effect sizes are based on GLMs with group and sex as fixed factors and age as a covariate. Ps < .05 are marked in bold.

The lesions partly overlapped the fMRI activation seen in healthy young adults (Fig. 2c) when contrasting words with letter strings, but only minimally affected cerebellar areas that were modulated by contextual predictability or violations of linguistic predictions (Moberget et al., 2014). We quantified lesion–activation overlap by computing the spatial correlation between the lesion overlap map and activation maps from the four contrasts of interest: *Scrambled* > *Letterstrings*, *Congruent* > *Scrambled*, *Incongruent* > *Congruent* and *Incongruent* > *Scrambled* (from Moberget et al., 2014). For these analyses, the 3D-images were first cropped by a cerebellar mask in order to prevent non-brain areas (0-valued in both maps) from artificially inflating correlations. The cropped images were transformed to 1-D vectors used to calculate a set of bivariate Pearson product moment correlations. Differences between correlation coefficients were evaluated by Fisher-transforming the r-values to z-values and then computing Steiger's z (Meng, Rosenthal, & Rubin, 1992), a statistical test that takes into account the overlapping nature of these correlations (as all activation maps were correlated with the same lesion overlap map). The lesion overlap map was moderately correlated (r = .40) with the activation pattern associated with the processing of random word sequences. In contrast, correlations with the activation patterns related to prediction generation and prediction errors were weak (all r-values < ±.07) Steiger's z tests confirmed that the difference between the first and the three latter correlation coefficients were highly significant (all p-values < .001).

3.3. Behavioral results from the fMRI-experiment

Overall accuracy was 94% in patients and 97% in controls, indicating that the task was not especially demanding, with all participants able to discriminate between the meaningful (*Congruent*) and meaningless (*Incongruent*, *Scrambled* and *Letterstring*) sentences. While response speed was not emphasized in the instructions, our previous results revealed systematic differences in reaction time (RT) across conditions. Hence, we analyzed RTs using repeated measures ANOVA with the factors Condition (4 levels; *Congruent*, *Incongruent*, *Scrambled*, *Letterstring*) and Group (2 levels: patients and controls). Reaction times (RTs) differed considerably across conditions, (F (3, 54) = 9.351, P < 0.0001). RTs were faster in the *Congruent* condition (mean: 834.3; SD: 221.3) compared to the *Incongruent* condition (mean: 1081.9; SD: 312.4). The means for the *Scrambled* (mean: 900.8; SD: 249.0) and *Letter string* conditions (mean: 859.3; SD: 261.7) fell between the means for the congruent and incongruent conditions. Mean reaction times were faster in patients (883.4; SD: 237.9) than in controls (954.8; SD: 229.4), but the effect of Group was not significant (F(1, 18) = .466, p = .503) nor was the Group × Condition interaction (F(3, 54) = 1.888, p = .143).

3.4. BOLD-activations related to general language processing

To identify a network associated with more general (non-predictive) aspects of language processing, we focus on the contrast of the *Scrambled* word condition to the *Letter String* control condition. This contrast was chosen – both in the previous and in the current study – since it allows us to compare meaningful linguistic stimuli to visually similar, but meaningless stimuli while equating stimulus predictability (absent for both stimulus types) across conditions. A network of primarily left lateralized cortical regions associated with linguistic processing (Price, 2010) showed greater activation in the *Scrambled* condition compared to the *Letter String* control condition. This general pattern was evident in the data for both patients and controls (Fig. 3a and b, Table 3). Directly comparing patient and controls revealed significant differences in bilateral superior temporal gyri and rolandic operculum (Fig. 3c

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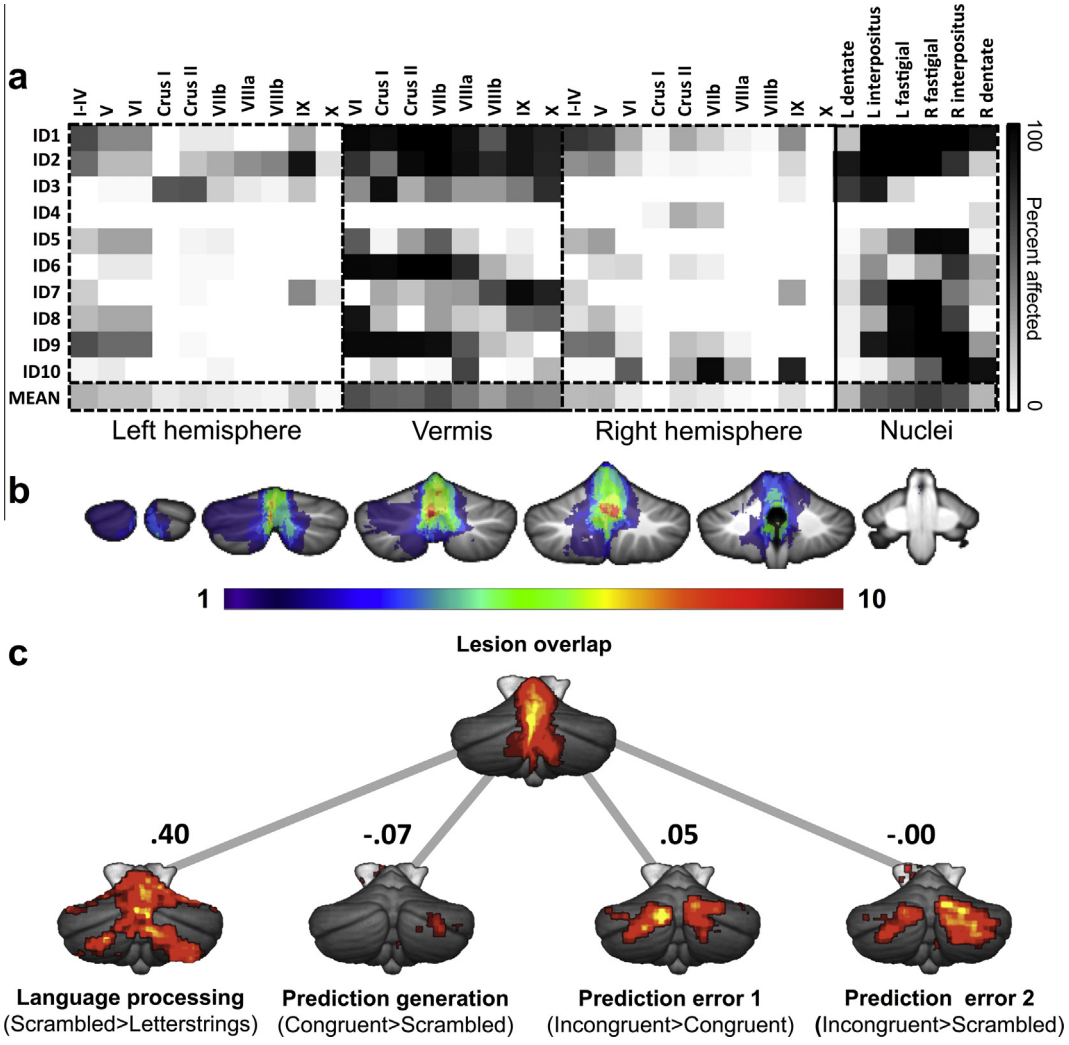

Fig. 2. (a) The fraction of cerebellar lobules and nuclei (columns) affected by the lesions in individual patients (rows) and mean affection of each region across all patients (bottom row). Label assignment is based on the probabilistic cerebellar atlas in the SUIT-toolbox (Diedrichsen, 2006). (b) Overlap of cerebellar lesions displayed on coronal sections of the SUIT template (Diedrichsen, 2006). The colorbar indicates the number of patients with lesions at a particular voxel. (c) Lesion overlap in cerebellar patients ($N = 10$) and cerebellar language-related activations from 32 healthy control subjects (Moberget et al., 2014) rendered onto the SUIT template. For the lesion overlap map the color scale ranges from 1 to 9 patients while the activation maps range in t-values from 2.75 to 7. Numbers give the correlation coefficients between the lesion overlap map and the significant cerebellar activations for each of the four experimental contrasts.

and d). While controls showed increased activity in these cortical areas in the Scrambled condition (positive values in Fig. 3d), the contrast estimates were not significantly different from zero in the cerebellar patients (Fig. 3d). As can be seen in Table 3, clusters showing significant group effects were seen bilaterally in the core region of primary auditory cortex (TE 1.0 and TE.1.1. (Morosan et al., 2001)), extending into ventral parts of the parietal operculum (OP 1, OP 3 and OP 4; (Eickhoff, Amunts, Mohlberg, & Zilles, 2006; Eickhoff, Schleicher, Zilles, & Amunts, 2006)) and posterior parts of the insula (Ig2; Kurth et al., 2010). While visual comparison of the activation maps in patients and controls suggest areas of increased frontal activation in patients and areas of increased activation in visual areas for controls, these were not significant in the direct comparison of patients and controls.

3.5. BOLD-activations related to prediction generation

The top two rows of Fig. 4 display results from the contrast examining prediction generation (*Congruent > Scrambled*). In patients this contrast revealed significant activations in bilateral supramarginal gyri as well as subcortical activations in the basal ganglia. The controls showed a similar pattern, but only a cluster in the left supramarginal activation reached statistical significance. No significant group effects were observed for this contrast.

3.6. BOLD-activations related to prediction error processing

The last four rows in Fig. 4 present results from the analyses examining responses to prediction violations. The activation patterns were similar in patients and controls for the contrast of *Incongruent* and *Congruent* conditions. For both groups, activations were larger in the incongruent condition in bilateral inferior frontal gyri and superior medial frontal gyri, and we did not observe any significant group effects. Contrasting the *Incongruent* over the *Scrambled* condition yielded similar patterns. For the patients, significant differences were observed in left inferior frontal gyrus, left basal ganglia structures and bilateral superior medial frontal gyri. The controls displayed a similar pattern, but with additional activations spreading into bilateral anterior temporal lobes. Directly comparing patients and controls revealed no significant differences.

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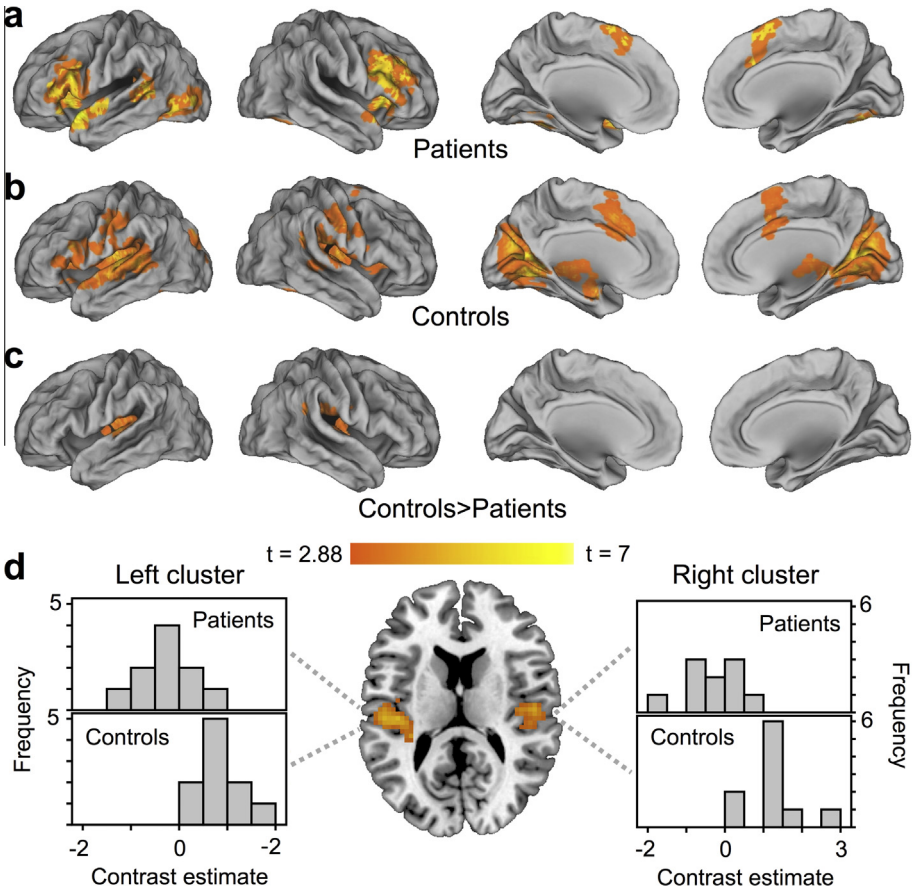

Fig. 3. Significant cerebral activations for the language localizer contrast (Scrambled > Letterstrings). Results for cerebellar patients (a), healthy controls (b) and significant group differences (c) are rendered on the cerebral surface using the Caret software package (Van Essen, 2012). Images are thresholded at $p < 0.005$ (uncorrected) and show clusters surviving cluster-level FDR correction for multiple comparisons ($q < 0.05$); (d): Group effects displayed on an axial slice and distributions of mean contrast estimates (in arbitrary units) for patients and matched controls for the two clusters.

Table 3
MNI coordinates and anatomical labels of significant group effects.

Contrast	Volume (mm^3)	q (corr.)	z	Coordinates			Anatomical labels
				x	y	z	
Controls > patients	4887	.003	4.30	51	−16	17	**24.7% in right OP 1 (29.3%),** 16.3% in right TE 1.0 (40.9%), 11.9% in right OP 4 (14.5%), 11.4% in right OP 3 (26.9%).
	4860	.003	4.27	−51	−19	8	**24.4% in left TE 1.0 (75.3%),** 12.7% in left insula (Ig2) (46.6%), 8.6% in left OP 4 (8.7%), 7.3% in left TE 1.1 (25.1%).
Patients > controls	–	ns	–	–	–	–	

Clusters showing significant activation differences between patients and controls. We present the volume of the cluster (thresholded at voxelwise $p < .005$, uncorrected), FDR-corrected cluster-level p-value, voxel z-values and MNI coordinates of the peak within each cluster. Probabilistic anatomical labels are taken from the Anatomy toolbox for SPM (Eickhoff et al., 2005; Eickhoff et al., 2006b; Eickhoff et al., 2007). Percentages outside of brackets denote the fraction of the cluster assigned to a probabilistic label, while percentages within brackets denote the fraction of the probabilistic label covered by the cluster. Anatomical labels in bold font correspond to the MNI-coordinates of peak cluster z-values.

4. Discussion

While a large body of neuroimaging studies report cerebellar activations during language tasks (Keren-Happuch et al., 2014; Stoodley & Schmahmann, 2009), the clinical literature provides a more ambiguous picture of cerebellar contributions to language (Alexander et al., 2012; Mariën et al., 2014; van Gaalen et al., 2014). Indeed, both the degree of language deficits following cerebellar damage and the functional role of the cerebellum in language processing remain contentious issues (Mariën et al., 2014). Here, we attempt to bridge this gap by testing the effect of focal cerebellar lesions on cerebral activations in a reading task previously shown to elicit distinct patterns of cerebellar activation patterns in healthy young adults (Moberget et al., 2014). The focus of that study had been on predictive aspects of semantic processing, employing contrasts focusing on prediction generation and prediction error. These contrasts revealed activations in the posterior cerebellar hemispheres (Crus I/II), as well as in a distributed cerebral network. An experimental contrast designed to map brain areas associated with more general (non-predictive) aspects of language processing *(Scrambled words > Letter Strings)* also revealed cerebellar activations, but these were in more medial regions. This latter contrast also revealed primarily left-lateralized cerebral activations in areas associated with language processing (e.g., left inferior frontal gyrus, left superior temporal gyrus). In the current study, we asked if the spatial distribution of the patients' lesions

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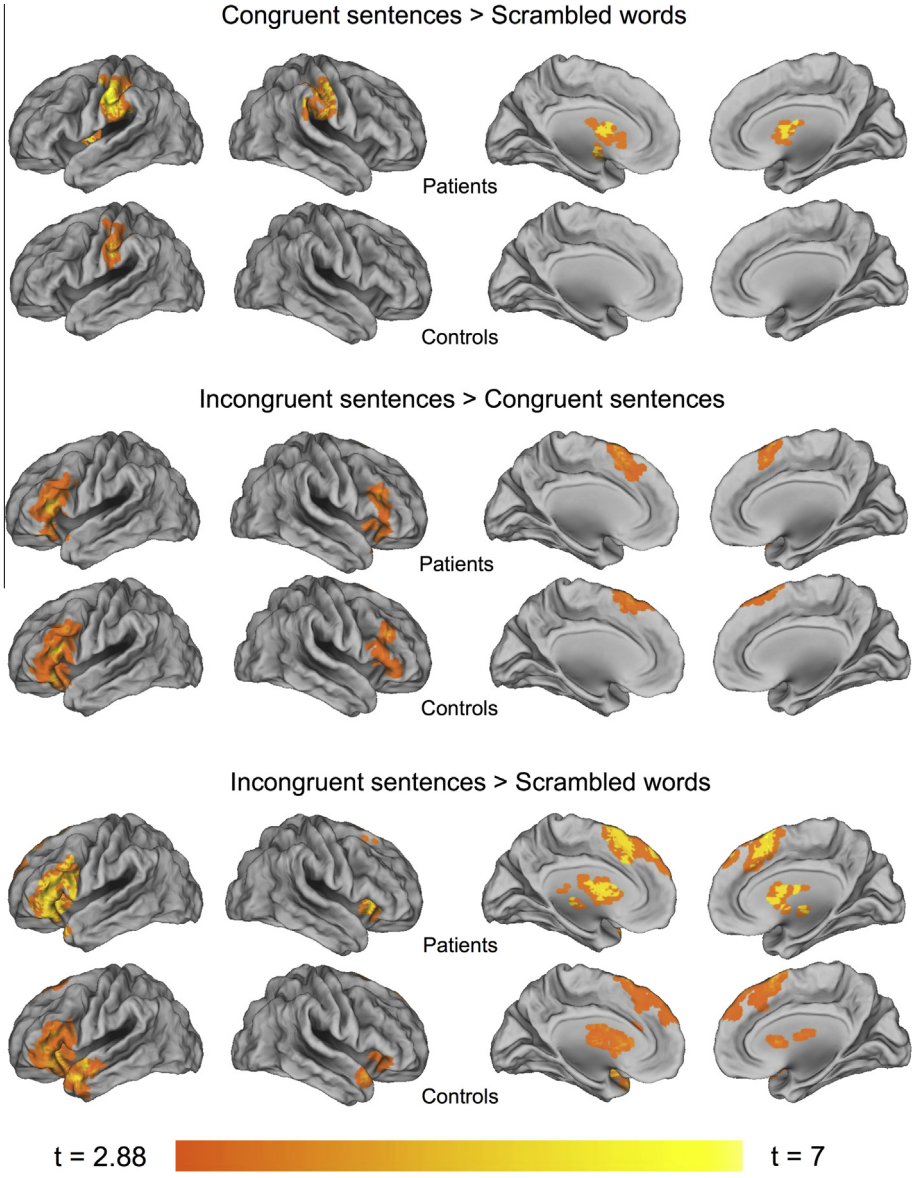

Fig. 4. Cerebral activation patterns for the contrasts targeting prediction (top two rows) and prediction error processing (bottom four rows). No significant group differences were observed for any of these contrasts.

would be related to contrast-specific changes in cerebral activations, relative to matched controls.

Given that the patients' lesions had minimal overlap with cerebellar regions sensitive to semantic prediction generation or prediction error processing, we did not expect significant group differences in the contrasts related to semantic predictability. This null prediction was confirmed. Of course, future studies including patients with focal lesions to cerebellar nodes of the cerebro-cerebellar networks associated with predictive aspects of semantic processing (lateral Crus I/II) will provide a much stronger test of the hypothesis that these cerebellar regions influence cortical activation during predictive language processing.

The patients' lesions did overlap with cerebellar regions activated in the experimental contrast designed to identify more basic, non-predictive aspects of language processing *(Scrambled words > Letter Strings)*. In line with this selective lesion–activation overlap pattern, group differences in cortical activation were only observed for this latter contrast. While the control participants showed increased activity in bilateral primary auditory cortex (and parietal operculum) in response to reading words relative to letter-strings, this difference was not seen in the patients. The patients did not show any significantly increased BOLD-activations relative to controls.

The group difference in activation of auditory cortex is surprising, given that both primate anatomy (Strick, Dum, & Fiez, 2009) and functional connectivity in humans (Buckner et al., 2011; Sang et al., 2012), suggest weak connections between the cerebellum and the primary auditory cortex. However, several neurophysiological studies have demonstrated short-latency (8–12 ms) modulation of auditory cortex responses following stimulation of the cerebellar vermis and fastigial nuclei in cats (Mitra & Snider, 1969; Teramoto & Snider, 1966; Wolfe, 1972). Furthermore, electrical stimulation of the deep cerebellar nuclei (interpositus) in primates led to BOLD-activations in primary auditory, as well as motor and premotor areas (Sultan et al., 2012). In humans, co-activation of several cerebellar regions, including the right paravermal Crus II affected in our patient sample, and primary auditory cortex is a reliable finding in auditory neuroimaging tasks (Petacchi, Laird, Fox, & Bower, 2005). Moreover, repetitive transcranial magnetic stimulation of the lateral cerebellum (Crus II)

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has been shown to modulate the steady-state auditory evoked potential (Pastor, Thut, & Pascual-Leone, 2006), localized to primary auditory cortex (Pastor et al., 2002). Finally, cerebellar pathology in humans has been shown to affect the modulation of evoked potentials that are assumed to be, at least in part, generated in the primary auditory cortex, including the P50 (Ghisolfi et al., 2004; Moberget et al., 2008), N100 (Knolle, Schröger, Baess, & Kotz, 2012; Knolle, Schröger, & Kotz, 2013) and mismatch negativity (Moberget et al., 2008).

What might be the functional significance of reduced auditory cortex activation in cerebellar patients? While we recognize that activations revealed in the contrast of random word sequences over consonant strings may be related to a wide range of linguistic processes (e.g., word recognition, processing of lexical phonology or processing of different graphemes), we consider two hypotheses that can serve as starting points for further research. First, the cerebellum might play a role in visual-to-auditory mapping. Reading involves a cross-modal mapping from visual to auditory representations (McNorgan, Awati, Desroches, & Booth, 2013; van Atteveldt, Roebroeck, & Goebel, 2009), with letter–speech sound associations being over-learned in literate adults (van Atteveldt et al., 2009). Previous studies have yielded a mixed picture concerning activation of primary auditory cortex during silent reading (Chan et al., 2014; Jäncke & Shah, 2004; Perrone-Bertolotti, Rapin, Lachaux, Baciu, & Lœvenbruck, 2014; Perrone-Bertolotti et al., 2012; Petkov & Belin, 2013; Price, 2012; Vartiainen, Liljeström, Koskinen, Renvall, & Salmelin, 2011; Wild, Davis, & Johnsrude, 2012). In one recent fMRI study (Wild et al., 2012), participants listened to degraded speech accompanied by matching or non-matching visually presented words. Crucially, matching visual-auditory pairings resulted in both increased intelligibility and increased activation in primary auditory cortex. Since the auditory stimuli were kept constant across conditions, the authors argue that this modulation of auditory cortex activation must reflect active prediction of auditory input based on the visual cues (Wild et al., 2012). We hypothesize that the cerebellum might be involved in this process, based on the idea that this structure serves a general role in real-time prediction (in this case of auditory features rather than semantic content). Supporting this notion, learning to pronounce pseudowords – i.e., acquiring new visual–auditory mappings – modulates activity in both primary auditory cortex and the cerebellum (Rauschecker, Pringle, & Watkins, 2008). Moreover, individual differences in visual–auditory mapping skill are associated with grey matter density in the cerebellum and the hippocampus (He et al., 2013).

A second hypothesis, one that is not incompatible with the mapping hypothesis, is that the cerebellum is involved in the generation and modulation of inner speech (Ait Khelifa-Gallois et al., 2015). Activations of auditory cortex during silent reading are often interpreted as reflecting inner speech (Perrone-Bertolotti et al., 2014). A cerebellar contribution here might be related to sub-vocal articulation (Chen & Desmond, 2005; Marvel & Desmond, 2012), the generation and modulation of auditory (phonological) information (Kirschen et al., 2008; Marvel & Desmond, 2012), or motor–auditory integration. In the current study, the reduced activation observed in the patients in both sensori-motor (opercular) and auditory cortex might reflect disruption of a network for inner speech. Interestingly, a recent study suggests that a region of the posterior operculum partly overlapping with the current cluster (OP4) plays a critical role in auditory–motor integration (Sepulcre, 2013).

As reviewed by Perrone-Bertolotti et al. (2014), people engage in inner speech during a range of cognitive functions, such as verbal working memory, planning, problem-solving, self-motivating, reading, writing, calculating and autobiographical memory. Notably, verbal working memory deficits and subtle problems with executive function are among the most consistent findings in studies of cognitive function following cerebellar lesions (Alexander et al., 2012; Timmann & Daum, 2007), replicated in our neuropsychological tests in the current study. These deficits could arise from disruption of inner speech (Ackermann, Mathiak, & Ivry, 2004); for example, it may make it be difficult to maintain the contents of working memory. Clinical evidence has supported a relationship between inner speech impairments and reduced working memory capacity in patients with cerebellar tumor resections (Ait Khelifa-Gallois et al., 2015). It should be noted that inner speech typically also activates an inferior frontal region associated with subarticulation and supramarginal gyri (Perrone-Bertolotti et al., 2014; Price, 2012), and is negatively affected by lesions to these areas (Geva et al., 2011). None of these key areas showed any significant group differences in the current study, at odds with an inner speech account (at least the articulatory component) of the current findings.

A deficit in fundamental processes as visual-to-auditory mapping or inner speech might be expected to cascade onto more complex linguistic processes, but we observed no group differences in contrasts designed to highlight cortical regions associated with generating linguistic predictions and processing violations of these predictions. However, current models of reading and language posit a multiplicity of mechanisms for translating visual stimuli to semantics (Richardson, Seghier, Leff, Thomas, & Price, 2011), auditory–motor integration (Sepulcre, 2013), and generating linguistic expectancies at different hierarchical levels (from phonology to semantics; (Pickering & Garrod, 2013). Thus, the language system as a whole may be relatively resilient to deficits in specific sub-processes.

The main limitations of the current study are the small sample size and the lack of standardized testing targeting the different cognitive processes underlying reading ability. Notably, a recent study employing formalized reading tests in a larger group of patients with cerebellar tumor resections ($N = 21$) observed significantly reduced reading accuracy, reading speed, reading comprehension and silent reading in patients relative to controls (Ait Khelifa-Gallois et al., 2015). In line with these findings, the individual scores on the CWIT-reading subtest showed slowed reading in four of the patients in the current sample (reading latencies > 2 SD slower than the control group mean). The behavioral task used in the scanner was designed to ensure attentive reading of the sentences while imposing modest demands on comprehension; thus, the lack of group differences on this behavioral measure is not surprising. Future studies using larger samples of cerebellar patients, and specifically targeting potential mechanisms such as visual-to-auditory mapping and/or inner speech, will be needed to provide stronger tests of the functional consequences of the abnormal activation patterns observed in the cortex following cerebellar pathology.

While groups were well matched on age and sex, we observed a significant group difference in estimated IQ. IQ is usually not affected following cerebellar pathology in adults (Alexander et al., 2012; Timmann & Daum, 2010), but moderate reductions have been observed following lesions acquired in childhood (Beebe, 2005; Rønning, Sundet, Due-Tønnessen, Lundar, & Helseth, 2005), suggesting an interaction between cerebellar insult and developmental stage (Alexander et al., 2012; Timmann & Daum, 2010). As such, the observed IQ differences likely reflect long-term effects of the cerebellar pathology in our sample, although it remains possible that the difference is related to our sample size and selection criteria. It is also worth noting that the areas typically associated with IQ differences (e.g., prefrontal cortex; Deary, Penke, & Johnson, 2010) overlap most extensively with brain regions identified in our contrasts targeting effects of predictability, where we did not observe any group differences.

In conclusion, compared to healthy controls, patients with focal cerebellar lesions showed reduced activations of auditory and

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opercular cortex when silently reading familiar words relative to viewing letter strings. In contrast, there were no group differences for experimental contrasts targeting linguistic prediction generation and prediction error processing. This dissociation is consistent with predictions based on the joint consideration of lesion overlap in our sample and cerebellar activations in healthy young adults on the experimental task. Thus, our results highlight the need for careful lesion mapping when investigating functional consequences of cerebellar pathology on cognitive tasks such as reading and semantic comprehension. Future studies, using larger patient samples and experimental tasks specifically targeting potential mechanisms, will be needed to elucidate the functional significance of the current findings.

Conflict of interest

The authors declare no competing financial interests.

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