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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. *P*s < .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