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Cerebellar rTMS disrupts predictive language processing

Elise Lesage¹, Blaire E. Morgan¹, Andrew C. Olson¹, Antje S. Meyer^{1,2}, and R. Chris Miall¹

The human cerebellum plays an important role in language, amongst other cognitive and motor functions [1], but a unifying theoretical framework about cerebellar language function is lacking. In an established model of motor control, the cerebellum is seen as a predictive machine, making short-term estimations about the outcome of motor commands. This allows for flexible control, on-line correction, and coordination of movements [2]. The homogeneous cytoarchitecture of the cerebellar cortex suggests that similar computations occur throughout the structure, operating on different input signals and with different output targets [3]. Several authors have therefore argued that this ‘motor’ model may extend to cerebellar nonmotor functions [3–5], and that the cerebellum may support prediction in language processing [6]. However, this hypothesis has never been directly tested. Here, we used the ‘Visual World’ paradigm [7], where on-line processing of spoken sentence content can be assessed by recording the latencies of listeners’ eye movements towards objects mentioned. Repetitive transcranial magnetic stimulation (rTMS) was used to disrupt function in the right cerebellum, a region implicated in language [8]. After cerebellar rTMS, listeners showed delayed eye fixations to target objects predicted by sentence content, while there was no effect on eye fixations in sentences without predictable content. The prediction deficit was absent in two control groups. Our findings support the hypothesis that computational operations performed by the cerebellum may support prediction during both motor control and language processing.

We recorded the eye movements of 65 participants while they listened to pre-recorded sentences and looked at static displays depicting the agent

and the direct object (the target) of the sentence, as well as three distracter objects which were not mentioned in the sentence (Figure 1A). In half the trials, the target object could be predicted from the verb (Prediction condition), in the other half such prediction was not possible (Control condition). We measured the time it took listeners to look at the target object (the target fixation latency) from the onset of the verb. Earlier studies using similar materials have shown that listeners are considerably faster to fixate the target object in the Prediction condition than in the Control condition [7]. In 22 participants, rTMS was applied to the right cerebellum between two blocks of Visual World task trials (for details on the materials, design, stimulus randomization, and TMS protocol see the Supplemental Information available on-line with this issue). If

the cerebellum is engaged in on-line linguistic prediction, the disruption of this mechanism should slow down target fixation when prediction is possible (Prediction trials). Conversely, when target prediction is not possible (Control trials) the disruption should not affect target fixation latency.

As hypothesized, participants were slower to fixate the target following cerebellar rTMS in the Prediction condition, but were not slowed in the Control condition (rTMS-by-Condition interaction: $F(1,21) = 8.848$, $p = 0.007$, repeated-measures ANOVA; Figure 1B). That is, disrupting function in the right cerebellum selectively impaired the prediction aspect of sentence processing in this task; other language processes were spared. This effect cannot be explained by changes in eye movement kinematics, which were not altered by rTMS (see Supplemental Information).

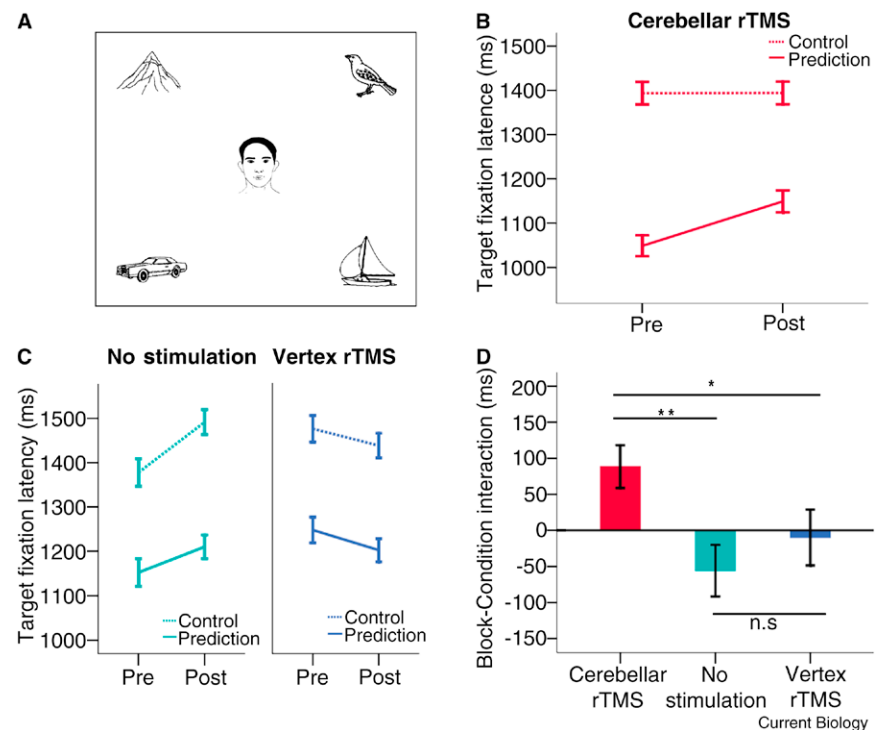


Figure 1. Stimulus example and eye movement analysis results.

(A) Example of a visual scene. In the Prediction condition (e.g. “The man will sail the boat”), the direct object of the sentence (the boat) can be predicted from the verb “sail” because it is the only object in the array plausibly related to that action. In the Control condition (e.g. “The man will watch the boat”), such prediction is not possible. (B) Target fixation latencies before and after rTMS to the right lateral cerebellum. Participants were slower to fixate the target in the Prediction condition (solid red), while fixation latency in the Control condition (dashed red) was unaffected. (C) Target fixation latencies in the No Stimulation condition (left) and the Vertex rTMS condition (right). There was no interaction between Block and Condition in either group. (D) Block-by-Condition interactions for the three groups. The hypothesized positive interaction is only evident in the cerebellar group (red), and is significantly different from the two control groups (green and blue), which do not differ from each other. (B–D) Error bars in all panels denote ± 1 standard error of the mean. *: $p < 0.05$; **: $p < 0.01$; n.s.: no significant difference.

To ensure that the slower fixation in the Prediction condition was not due to effects of fatigue, familiarity with the task, or an effect of rTMS not specific to the cerebellum, we performed two control experiments. One group of participants ($n = 21$) received rTMS over a control site, the vertex, and another group ($n = 22$) received no TMS stimulation at all. Repeated-measures ANOVAs showed that the Block-by-Condition interaction was absent in both the Vertex Stimulation control condition ($F(1,20) = 0.064$, $p = 0.802$) and the No Stimulation control condition ($F(1,21) = 2.461$, $p = 0.132$). An analysis using data from all three groups revealed a significant three-way interaction ($F(2,62) = 4.548$, $p = 0.014$). Planned comparisons between the groups were carried out using t-tests and demonstrate that the Block-by-Condition interaction in the cerebellar rTMS group differed significantly from that in both the No Stimulation control group ($t(42) = 3.111$, $p = 0.003$) and the Vertex rTMS control group ($t(41) = 2.021$, $p = 0.050$), while the interaction did not differ significantly between the two control groups ($t(41) = 0.875$, $p = 0.387$; **Figure 1C,D** and Supplemental Information). We can therefore attribute the impaired performance in the Prediction condition to disruption of neural operations by rTMS over the right cerebellum. There is no reason to believe that rTMS effects on neighboring structures, including the right occipital lobe, could be responsible for this selective deficit in predictive processing.

Finally, to ensure the fixation latency effects observed were not due to an inability to perform the task following cerebellar rTMS, we also analyzed error rates before and after rTMS, and between the two conditions after cerebellar rTMS. If the participants were unable to identify the spoken words, or if the information flow between language centers involved in sentence comprehension and oculomotor centers involved in object fixation was disrupted, this would be reflected in the fixation behavior of participants. Neither of the error measures differed significantly from the first to the second block or between conditions after rTMS (see Supplemental Information). Hence, cerebellar rTMS resulted in an equally accurate, but delayed target fixation, consistent

with the loss of the temporal advantage conferred by a short-term prediction.

It is thought the cerebellum contributes to fast and flexible motor control by predicting the sensory consequences of movements on a fine timescale, and that these predictions are available before visual or proprioceptive feedback from the executed actions [2,4]. This cerebellar 'forward model' prediction, based on an efferent copy of motor commands, allows for rapid error detection and correction, for motor coordination and motor planning [2,4,6]. Like motor control, language comprehension is highly time sensitive, and listeners must process the spoken input on-line, at a rate set by the speaker. While they cannot anticipate with certainty what will be said, they can often predict future sentence content based on shared linguistic and world knowledge [7]. A predictive process similar to forward modeling in motor control [4] could therefore contribute to the speed and efficiency of language processing [9].

We cannot yet say how these predictions are made; they might directly predict semantic content or instead they might predict internalized speech production that could indirectly support comprehension [9]. There is evidence that the right lateral cerebellum (lobule HVII/Crus I) is part of the verbal working memory and language system [1,10] (see also Supplemental Information). In addition, the right lateral cerebellum is connected with cortical language and higher cognitive areas such as Broca's area and the dorsolateral prefrontal cortex [1,5,8]. So we speculate that input to the right cerebellum from connected language structures, possibly Broca's area, would provide an 'efferent copy' of internalized speech, from which the lateral cerebellum would predict future speech output. These predictions then would feed back to frontal cortical language areas to facilitate processing, in parallel to cortico-cortical inputs. Several aspects of the predictive role of the cerebellum in language processing should be further investigated. There is evidence that some aspects of language processing are embodied, and interact with motor control processes. We cannot yet say whether the effect we report here

also shows sensitivity to action-related verbs. In our study, the predictions were based on the verb meanings. Future research should also investigate whether other types of prediction based, for instance, on syntactic or pragmatic information also implicate the cerebellum.

In summary, we have shown that language processing is delayed in a predictive language task when right cerebellar function is disrupted. Our data suggest that the cerebellar theory of predictive motor control can be extended to the nonmotor cerebellum. This adds support to the notion that similar computations are performed across the structure, with different inputs and with different output targets.

Supplemental Information

Supplemental Information includes one figure and Supplemental Experimental Procedures and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2012.07.006>.

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INVENTORY

Supplemental Data

Figure S1: Error rates for the cerebellar rTMS group between blocks, and between conditions after cerebellar rTMS.

Supplemental Experimental Procedures

1. We provide a description of the materials, task, and stimulation protocol used in this study.
2. We present Supplemental Analysis and Results sections, detailing the main statistical analysis, as well as additional analyses.
3. A final section provides background information on cerebellar involvement in language.

SUPPLEMENTAL FIGURE

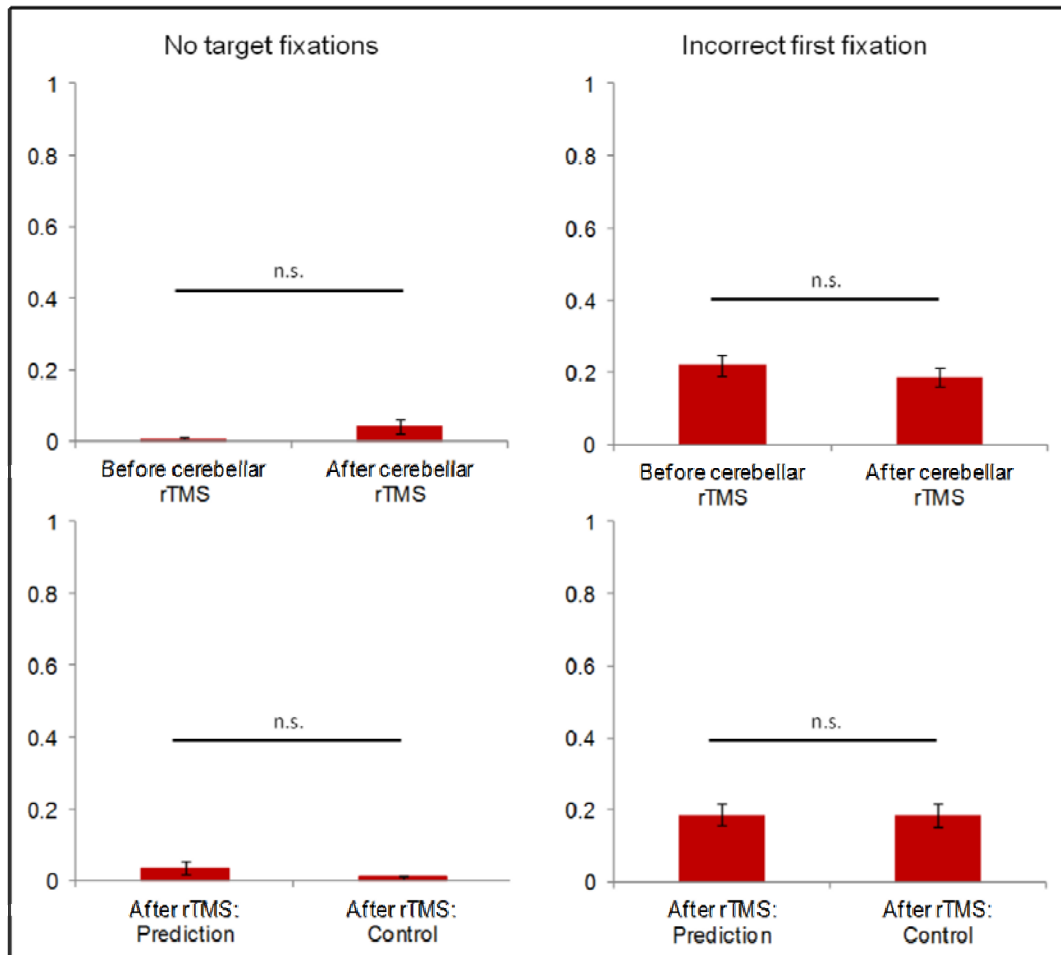


Figure S1: Error analysis.

Average proportion of trials where the target object was not fixated at all (left column) and the average proportion of trials where a non-target object was fixated prior to the target object (right column). The upper row is collapsed across both conditions; the lower row separates the Prediction condition from the Control condition after cerebellar rTMS. On both measures, there was no change in participants' performance following cerebellar rTMS, nor did they perform better or worse in the Prediction condition following rTMS. These data indicate that the participants' accuracy in identifying the target words was not affected by the stimulation.

SUPPLEMENTAL EXPERIMENTAL PROCEDURES

1. Supplemental Methods

All methods and procedures were approved by the local ethics committee, and written informed consent was obtained for each participant.

Participants

All participants were right-handed native English speakers recruited from the University of Birmingham student population, and had no contra-indications for TMS, as assessed by a standard screening form (http://prism.bham.ac.uk/downloads/TMS_screening_form.pdf). The 65 participants (mean age = 20.5 years, 20 male) received course credit or financial compensation for their time.

Task details

At the beginning of each Visual World trial, four objects appeared, one in each corner of the screen. Participants were instructed to look at all objects, think about what they were and where they were on the screen. After 3000ms, the face of the agent (a man, woman, boy or girl) appeared in the middle of the screen, and as soon as the participant fixated the face of the agent, a pre-recorded sentence was played over headphones. Participants were instructed to look at what was mentioned in the sentence.

Materials

Auditory stimuli were 64 spoken sentences, constituting 32 items. Sentences were spoken by an English native speaker with a neutral accent. They were digitally recorded as .wav files and played over standard headphones. Of the 64 sentences, 28 were taken from Altmann and Kamide [1]. The remaining 36 sentences were newly created.

Each item consisted of one sentence in the Prediction condition and one sentence in the Control condition. The only difference between Prediction and Control sentences was the

verb, which could refer to only one of the objects in the display (Prediction condition), or to any of the four objects in the display (Control condition). The display was identical in both conditions. The two verbs were matched for frequency of occurrence using the CELEX data base [S1].

Randomization

The 32 items were divided across two blocks of 16 items. The Prediction and Control variant of each item appeared in the same block so that the eye movements before and after rTMS stimulation could be compared within participants and within items. The order of the blocks was counterbalanced between participants. Within each block, the presentation of the items was pseudorandom, such that the Prediction and the Control version of the sentence pair were never presented adjacently.

Eye tracking

Eye movements were recorded using a desk-mounted Eyelink 1000 apparatus sampling the right eye at 1000 Hz. Each block was preceded by a 12 point eye tracker calibration. Drift correction was performed between trials. Each Visual World block lasted under 10 minutes.

Stimulation protocol

TMS stimulation was delivered using a Magstim Rapid apparatus and lasted 10 minutes. There was less than two minutes between the end of the stimulation and the start of the next experimental block. In the two participant groups where TMS pulses were delivered, the stimulator intensity was set at a fixed level of 55% of maximum stimulator output (MSO). We opted to use a fixed intensity rather than an intensity proportional to motor threshold, as primary motor cortical excitability is uncorrelated to the excitability of tissue elsewhere in the brain [S2, S3].

Cerebellar rTMS

The stimulation site was 1cm down and 3cm to the right from theinion. This is a site frequently used to stimulate lateral areas of the cerebellum [S4] and data from our lab using a large number of structural MRI scans has shown that this location on the scalp is closest to cerebellar tissue. The target site was stimulated at a fixed 55% of maximum stimulator output intensity with a double-cone coil for 10 minutes at 1Hz (600 pulses). Low-frequency rTMS has been shown to produce LTD-like after-effects in the targeted tissue for a period lasting up to the length of the stimulation [S5]. Prior to the stimulation, one single pulse was delivered in order to familiarize the participant with the sensation, and to allow them the opportunity to withdraw their consent prior to the rTMS stimulation.

Vertex rTMS control

The control stimulation site was taken as the Cz (the vertex), measured as the mid-point between the two external auditory canals in the transverse plane and the mid-point between inion and nasion in the saggital plane. The control site was stimulated at a fixed 55% of maximum stimulator output intensity with a flat figure-of-eight coil for 10 minutes at 1Hz (600 pulses). Prior to the stimulation, one single pulse was delivered in order to familiarize the participant with the sensation, and to allow them the opportunity to withdraw their consent prior to the rTMS stimulation.

No Stimulation control

Participants in the No Stimulation group were given instructions and explanations as if they were going to receive cerebellar rTMS. After the first Visual World block, they were informed that no TMS pulses would be delivered. However, the cerebellar stimulation site was determined and the double-cone coil was placed over this site for 10 minutes, without activation of the coil.

2. Supplemental Analysis

The dependent variable used was the target fixation latency; the time from the onset of the verb to the onset of the first fixation of the target object (the object of the sentence). We analysed fixations from 400ms after verb onset onwards, as it would take the participant at least 400 ms to understand the verb and initiate a saccade [S6, S7]. The reported latencies are measured from verb onset. Trials where no target fixation was made before 3500ms after verb onset were discarded from the latency analysis. Repeated measures ANOVAs and mixed effect modelling were performed on the fixation latencies (see below). In addition to the analyses of fixation latencies, we also compared error rates and several eye-movement kinematic parameters (average saccade velocity, peak saccade velocity, and saccade duration) before and after cerebellar rTMS using paired t-tests.

Repeated measures ANOVA

Repeated measures ANOVAs with fixed factors Block (levels Pre- and Post TMS) and Condition (levels Prediction and Control) and with participants as a random variable were conducted for each of the three groups of participants using SPSS software.

Mixed Model Analysis

It has been proposed that a linear mixed model approach is a more appropriate analysis strategy for this type of psycholinguistic data [S8]. The specific items used in this study represent a subsection of a larger population of possible experimental items, and could be treated as a random factor in addition to the random factor Participant. A repeated-measures ANOVA does not take these issues into account.

Therefore, in addition to the analyses of variance we performed linear mixed effect modelling on the fixation latency data using the lme4 package in R. This allowed us to enter both Participant and Item simultaneously as random effects [S9, see also S8], which is not possible in analyses of variance. Condition and Block were entered as fixed effects. For this

analysis, Block was treated as a time-varying variable, with values 0 for the first block, and 1 for the second block. A model selection strategy using likelihood ratio tests was used to find the best fitting model with the least parameters [S8]. When the most appropriate random effects structure was selected, models with different combinations of fixed effects were compared.

Error rate comparison

To ensure the fixation latency effects observed were not due to an inability to perform the task following rTMS, we also analysed error rates before and after cerebellar rTMS, and between the two conditions after cerebellar rTMS. If the participants were unable to identify the spoken words, or if the information flow between language centres involved in sentence comprehension and oculomotor centres involved in object fixation was disrupted, this would be reflected in the fixation behaviour of participants. "No-fixation" trials were defined as trials in which the correct target object was not fixated within 3500 ms; these trials have been excluded from the analysis of fixation latencies. We also determined the proportion of "error" trials: those in which the target was not the first object fixated, but where valid target fixation latency was measured within the trial duration; these trials have been included in the latency analyses.

Supplemental Results

Repeated-measures ANOVA

While the Cerebellar rTMS group showed a significant interaction between Block and Condition ($F(1,21) = 8.848$, $p = 0.007$; see main article), this interaction was absent in both the Vertex Stimulation control condition (Block-by-Condition interaction: $F(1,20) = 0.064$, $p = 0.802$; Repeated-measures ANOVA) and the No Stimulation control condition (Block-by-Condition interaction: $F(1,21) = 2.461$, $p = 0.132$; Repeated-measures ANOVA). An analysis using data from all three groups revealed a significant three-way interaction (See main article).

Eye movement kinematics

None of the measured eye movement variables showed any difference after cerebellar rTMS. Paired t-tests for average saccade velocity ($t(21) = 1.26$, $p = 0.222$), peak saccade velocity ($t(21) = -0.04$, $p = 0.972$), and saccade duration ($t(21) = -1.64$, $p = 0.116$) did not reach significance, indicating that there were no TMS-induced effects on eye movement kinematics, and ruling these out as a possible cause of post-TMS changes in target fixation latencies.

Mixed Model Analyses

The additional linear mixed model analyses revealed the same pattern of results as the ANOVA approach reported in the main article and above. In the Cerebellar Stimulation group, model comparison favoured a model with a Block-by-Condition interaction against the simpler model without an interaction ($\chi^2 = 4.100$, $p = 0.043$). In the Vertex Stimulation control group ($\chi^2 = 0.013$, $p = 0.908$) and in the No Stimulation control group ($\chi^2 = 1.044$, $p = 0.307$), the model with the interaction was not preferred, and therefore the simple, no interaction model should be assumed. The preferred random effects structure included Item as a random effect on the intercept, and Participant as a random effect on both intercept and slope.

Error rate analysis

Pair-wise t-tests comparing the number of errors before and after cerebellar rTMS revealed no significant effects, with a trend towards fewer errors after rTMS, possibly due to greater familiarity with the task (Paired t-test: $t(21) = 1.916$, $p = 0.069$; see Figure S1, right column). Following rTMS, the error rates did not differ between the two predictive conditions (Paired t-test: $t(21) = -0.075$, $p = 0.941$). When comparing trials where no fixations to the target were made, no significant differences arose between blocks before and after cerebellar rTMS (Paired t-test: $t(21) = -1.867$, $p = 0.076$), or between the two predictive conditions following

cerebellar rTMS (Paired t-test: $t(21) = -1.336$, $p = 0.196$; Figure S1, left column). These results demonstrate that participants were equally able to identify the target words and make corresponding eye movements. This further indicates that the observed rTMS-by-Condition interaction was due to a deficit in prediction, which resulted in slower fixation of the target on Prediction trials.

3. Supplemental information: Involvement of the cerebellum in language processing

A considerable body of evidence shows cerebellar involvement in language. Below we briefly review neuropsychological evidence from cerebellar lesions and dyslexia studies, as well as evidence for connectivity between cortical and cerebellar language areas, and neuroimaging studies in healthy control participants.

Patients with cerebellar lesions may present with problems with lexical access and syntax [S10], and speech production deficits [S11]. These deficits are have been interpreted as a failure of a cortico-cerebellar loop, which includes frontal and cerebellar language areas [S12, 8]. Such accounts are consistent with the idea that cortico-cerebellar loops support higher-level processes [S13].

Dyslexia has been linked to cerebellar deficits [S14, S15]. Eckert et al. [S16] analysed structural MRI scans of dyslexic children and controls, and found that the volume of the pars triangularis (Broca's area) and the right anterior cerebellum distinguished dyslexics from non-dyslexics. As in the lesion literature, this evidence is consistent with a higher-order cortico-cerebellar language system.

Cortical language areas, particularly Broca's area, have been found to be connected to the cerebellum. Patients with right cerebellar lesions show selective hypoperfusion in Broca's area [8]. A recent fMRI study of functional connectivity found strong bidirectional connectivity between the right cerebellum and both left inferior frontal gyrus and left middle temporal gyrus [S17]. Evidence from resting state functional connectivity studies demonstrates

connections between frontal, parietal and temporal areas and the lateral cerebellum [S18, S19].

In whole-brain neuroimaging studies of language in healthy participants, right cerebellar activity is often found. PET and fMRI studies of word generation [S20, S21], word stem completion [S22, S23], verbal fluency [S24], and semantic judgment [S25, S26, S27, S28, S29] elicit activity in the right cerebellum, along with cortical language areas such as the left inferior frontal gyrus and the left middle temporal gyrus. In a review of 100 fMRI studies on language [S30] semantic processing was found to activate left cortical language regions and the right cerebellum. Recently, Fedorenko et al., [S31] validated an fMRI language localizer, designed to detect language areas in individual subjects. The right cerebellum was amongst the regions which reliably (on an individual subject basis) responded to sentences versus non-word strings, whether there was a motor task component or not, and whether the stimuli were presented visually or aurally. While many of these studies do include motor aspects, these are controlled for in the contrasts used (i.e. there is an equal amount of covert speech or button presses in each condition). In a quantitative meta-analysis of various tasks that elicit cerebellar activation, language tasks were located to the right lateral cerebellum [S32]. These right lateral regions, distinct from medial regions controlling eye movements, were the target of our study.

To the best of our knowledge, no fMRI or EEG studies have investigated predictive language processing in the cerebellum. In fMRI studies of semantic prediction and priming, the cerebellum is rarely imaged or analysed. If cerebellar activations are found, these tend not to be discussed [S30, S33]. EEG signals from the cerebellum are very difficult to obtain due to its anatomical location. As far as we know, no EEG language studies have investigated the cerebellum. However, an ERP study by Dien et al. [S34] has localized a "meaningfulness" component to the right cerebellum, consistent with a cerebellar role in lexical access. Unfortunately, the exact source location is difficult to pinpoint using standard source localisation algorithms, as Dien and colleagues [S34] point out.

The present literature supports for a role for the right cerebellum in semantic processing, which is independent of modality in input (acoustic or visual stimuli) and output (overt speech, covert speech, button presses). Cerebellar lesions tend not to result in aphasic symptoms, but instead cause relatively mild impairments. No imaging studies have investigated a cerebellar role in linguistic prediction specifically, but the present literature is consistent with a cerebellar role in feedforward linguistic prediction, as has been proposed by Pickering and Garrod [10]. This hypothesis was therefore tested in our study.

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