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The cerebellum and embodied semantics: evidence from a case of genetic ataxia due to *STUB1* mutations

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Abundant research on lexicosemantic processing indicates that damage to movement-related regions (the motor and premotor cortices, Broca's area and the basal ganglia[1]) distinctively impairs processing of action verbs, that is, verbs denoting bodily motion. Moreover, such deficits could be hereditary,[2] suggesting an association with genetic factors. We, thus, hypothesised that genetically based deterioration of other motor regions could involve similar impairments. In particular, through a combination of structural and functional MRI (fMRI) with genetic and behavioural analysis, this case study indicates that distinctive action-verb deficits can also be linked to genetic mutations affecting the cerebellum, a key motor hub implicated in balance, posture and movement coordination. Accordingly, in line with the embodied cognition framework, our data illuminate a potential functional specialisation of the cerebellum within the lexicosemantic domain.

To test our hypothesis, we profited from access to a unique case of genetic ataxia and assessed action-verb processing together with cerebellar atrophy and related functional connectivity. The patient is a 26-year-old, Spanish-speaking male, with 13 years of education and a normal score (26/30) on the Montreal Cognitive Assessment (MoCA). He was diagnosed with cerebellar ataxia plus myoclonus, and exome sequencing revealed novel compound heterozygous mutations in the *STUB1* gene[3] (see online supplementary appendix e-1). His condition is characterised by severe dysarthria, action and postural tremor in the upper limbs, abnormalities of manual and facial movements and progressive disturbances of balance and gait.

The patient's neurocognitive profile was compared with that of six healthy male participants with no history of neuropsychiatric conditions. This sample had a mean age of 24.17 (SD=2.48), an average of 15 (SD=1.55) years of education and a mean score of 26.67 (SD=1.51) on the MoCA. Crawford's modified two-tailed t-tests (see online supplementary appendix e-2) showed that the patient and the controls were comparable in all these variables (age: t=0.68, p=0.52; years of education: t=−1.20, p=0.29; MoCA score: t=−0.41, p=0.7). All participants provided written informed consent. The study was approved by the institutional ethics committee.

Subjects performed a lexical decision task involving 80 real words (20 action verbs, 20 abstract verbs, 20 manipulable nouns, 20 abstract nouns) and 80 legal pseudowords (see online supplementary appendix e-3). Importantly, this paradigm has proven robust to reveal selective action-verb deficits in other motor disorders, such as Parkinson's disease.[4] After the task, resting-state recordings were obtained in a 1.5-T Phillips Intera scanner with a standard head coil, as in ref. 5 (see online supplementary appendix e-4.1). Behavioural data of the patient and controls were compared with Crawford's modified two-tailed t-test (see online supplementary appendix e-2). The patient's global atrophy pattern was established via voxel-based morphometry (VBM), as in ref. 6 (see online supplementary appendix e-4.2). Resting-state fMRI images were slice-time corrected, realigned, normalised and smoothed on DPARSF software, as in ref. 6 (see online supplementary appendix e-4.3). Additionally, we used seed analysis to compare connectivity among cerebellar networks between the patient and controls. The seed was established on the patient's highest atrophy peak. Voxel-wise connectivity was compared between the patient and controls with two-sample t-tests (p=0.001 uncorrected, extent threshold=50 voxels), as in ref. 5 (see online supplementary appendix e-4.4). Finally, we calculated the overlap between the patient's atrophy pattern and expression of the *STUB1* gene (see online supplementary appendix e-4.5).

Behaviourally, the patient was selectively impaired for action verbs, with relatively preserved processing of all other word types (figure 1A; see online supplementary table e-1). His maximum peak of atrophy, relative to controls, markedly involved the bilateral cerebella and extended to fronto-insulo-temporal regions (figure 1B; see online supplementary table e-2). Cerebellar functional networks differentiated the patient from controls, mainly in temporoparietal and frontal hubs (figure 1C; see online supplementary table e–3). The patient's atrophy overlapped with reported peaks of expression of the *STUB1* gene (bilateral cerebellar locations, temporal and fusiform gyri; figure 1D; see online supplementary table e–4).

To our knowledge, this is the first report of a selective, genetically driven action-verb impairment associated with cerebellar compromise. Within the lexicosemantic domain, The patient showed a selective deficit for this verb class, despite his relatively preserved cognitive skills. VBM data confirmed major bilateral atrophy of the cerebellum, suggesting that this region is part of the action-verb network proposed in previous research.[1 4 7]

Although the general role of the cerebellum in linguistic processing is well established,[8] our results specify that this region's lexicosemantic functions may include a differentially critical role for embodying action-verb information. Interestingly, as in previous studies,[4 7] the semantically driven effect observed in the patient emerged during a shallow processing task. Accordingly, the cerebellum may distinctively contribute to grounding action information even when conscious access to meaning can be bypassed for task completion. Together with evidence that action

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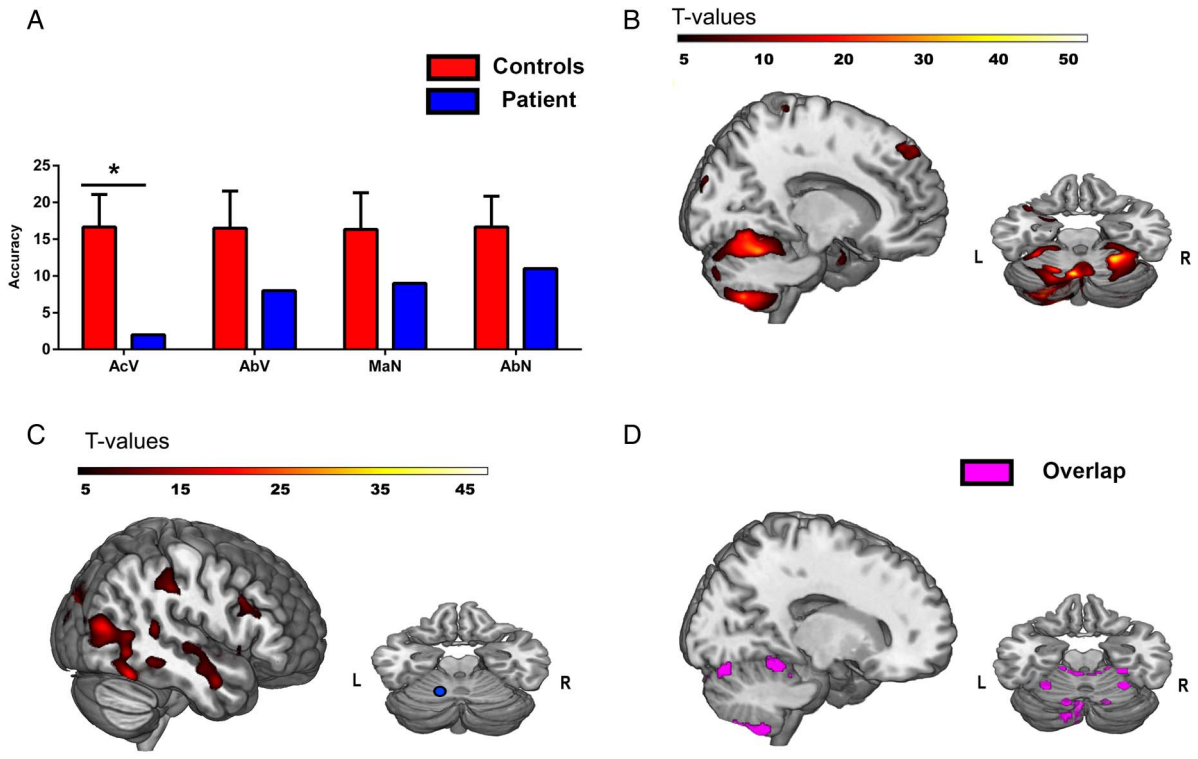

Figure 1 Behavioural and imaging results of the patient relative to controls. (A) Behavioural performance. Lexical decision results indicate a selective deficit for action verbs. AcV, action verbs (p=0.03); AbV, abstract verbs (p=0.18); MaN, manipulable nouns (p=0.23) and AbN, abstract nouns (p=0.26). (B) Atrophy pattern. Voxel-based morphometry results revealed a global atrophy pattern markedly involving the left and right cerebella, in addition to insular, frontal and temporal regions. (C) Functional connectivity alterations. Functional connectivity results revealed altered connectivity between peak atrophy site in the cerebellum (x=−17, y=−60, z=−20) and in both temporoparietal and frontal regions. (D) Gene atrophy overlap. Overlap between atrophied areas and sites of expression of the *STUB1* gene. Overlap was marked in multiple cerebellar locations and also in the fusiform and superior temporal gyri.

verbs are specifically compromised following lesions to other motor hubs,[1] our findings indicate that category-specific semantic impairments may be associated with damage to any neural region subserving a relevant experiential domain.

Moreover, aberrant cerebellar connectivity involved atrophied regions implicated in motor activity (for example, right frontal gyrus[9]) and disembodied semantic processes (for example, left temporoparietal regions[7]). Hence, action verbs seem to engage distributed neural networks which allow binding embodied and amodal conceptual information.[7] This supports the view that embodied cognitive functions related to the cerebellum actually rely on widespread interactions with relevant sensorimotor (and even higher level) mechanisms.[8]

Finally, the uniqueness of the patient's genetic mutation[3] offers novel insights into the biology of language. Crucially, the regions where the *STUB1* gene is expressed greatly overlapped with cerebellar and temporal atrophy in the patient. Thus, although this gene has a widespread expression across the brain (and the coordinates we used need not be identical for every individual), it could be associated not only with the development of motor skills but also with subtle aspects of lexicosemantics and with the role of the cerebellum in embodied cognitive evolution.[8] This observation challenges the quest for 'a language gene': even if specific genes, such as *FOXP2*, seem crucially related to linguistic development, a domain as complex and multidimensional as language could hardly be related to a single gene.[10]

In brief, evidence from this unique case shows that the cerebellum and its connections to semantic- and motor-related cortical regions are distinctively involved in processing of action verbs relative to other word classes, suggesting that embodied cognitive mechanisms may rely on any of the regions and networks supporting their experiential foundation. It would thus seem that the motor networks subserving action-verb processing extend beyond the cortical and subcortical extrasylvian hubs documented so far.[4 7] Moreover, our results offer explicit insights into the possible genetic basis of embodied lexicosemantics. Note, however, that our findings do not rule out critical contributions of the cerebellum to other language domains. Indeed, motor network damage consistently brings about syntactic deficits,[4] let alone articulatory difficulties such as dysarthria. Moreover, although the patient's scores were significantly poor only for action verbs, his performance was also suboptimal for the other lexical categories. Thus, even if the cerebellum is distinctively involved in the grounding of action semantics, this should be understood as a specialisation within its general contributions to lexical processing at large. Finally, while we only assessed receptive lexical skills, it would be crucial to further test our hypothesis via language production tasks. In sum, with its findings and open questions, this study paves the way for promising new research into the role of cerebellar structures in high-order domains.

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