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Cerebellum and Cognition: Evidence for the Encoding of Higher Order Rules

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Converging anatomical and functional evidence suggests that the cerebellum processes both motor and nonmotor information originating from the primary motor cortex and prefrontal cortex, respectively. However, it has not been established whether the cerebellum only processes prefrontal information where rules specify actions or whether the cerebellum processes any form of prefrontal information no matter how abstract. Using functional magnetic resonance imaging, we distinguish between two competing hypotheses: (1) activity within prefrontal-projecting cerebellar lobules (Crus I and II) will only be evoked by rules that specify action (i.e. first-order rules; arbitrary S–R mappings) and (2) activity will be evoked in these lobules by both first-order rules and second-order rules that govern the application of lower order rules. The results showed that prefrontal-projecting cerebellar lobules Crus I and II were commonly activated by processing both first- and second-order rules. We demonstrate for the first time that cerebellar circuits engage both first- and second-order rules and in doing so show that the cerebellum can contribute to cognitive control independent of motor control.

Keywords: cerebellum, cognition, fMRI, prefrontal cortex, rule retrieval

Introduction

Early theories of cerebellar function proposed that the cerebellum plays a key role in motor learning and in the sensory guidance of action (Holmes 1939; Marr 1969; Albus 1971; Stein and Glickstein 1992; Glickstein 1998; Wolpert et al. 1998; Ito 2000; Doyon et al. 2003). There is also a growing body of functional and anatomical evidence in both humans and nonhuman primates, which suggests that in addition to processing information from the primary motor cortex, the cerebellum also processes "nonmotor" information originating from the prefrontal and posterior parietal cortices (reviewed in Strick et al. 2009; Ramnani 2011). However, it is not yet clear to what end the cerebellum processes information originating from the prefrontal and posterior parietal cortices. Does the cerebellum only process information originating from the prefrontal/parietal cortex when it is paired with an action, or is it the case that the cerebellum will process any form of prefrontal or parietal information, no matter how abstract, in an effort to automate processes within these cortical regions (Ramnani 2006; Balsters and Ramnani 2011)? Anatomical evidence suggests that the latter may be the case, but to our knowledge, no neuroimaging study has specifically investigated whether cerebellar activity is present during the processing of increasingly abstract stimuli.

In this paper, we define increasing levels of abstraction in terms of increasing relational integration, that is, increasing the number of steps or rules necessary to execute a specific response increases the level of abstraction (see Badre and D'Esposito 2009). It has been suggested that increasingly abstract stimuli are processed in increasingly anterior portions within the frontal lobe (Miller and Cohen 2001; Ramnani and Owen 2004; Petrides 2005; Koechlin and Summerfield 2007; Badre and D'Esposito 2009). This rostrocaudal gradient extends from the central sulcus (i.e. primary motor cortex; area 4) through to the anterior prefrontal cortex (area 10), which is active during the most abstract and cognitively demanding tasks such as generating and maintaining subgoals (Ramnani and Owen 2004; Badre and D'Esposito 2007, 2009; Koechlin and Summerfield 2007). In between these two extremes are the premotor cortex (area 6; anterior to the primary motor cortex), which encodes information for preparatory set and is essential to the acquisition of first-order rules (Petrides 1982; Halsband and Passingham 1985; Wise 1985; Toni et al. 1999; Balsters and Ramnani 2008), pre-PMd [area 8; anterior to the dorsal premotor cortex (PMd)], which is selectively activated by more abstract hierarchical mappings (Picard and Strick 2001; Badre and D'Esposito 2007; Badre et al. 2010), and areas 9, 46, and 9/46, which encode increasingly abstract information including rules (Freedman et al. 2001; Wallis et al. 2001) and monitor information in working memory (Petrides 1994; Fuster 1997; Funahashi 2001). These areas are interconnected to form a hierarchically organized network in which executive control is achieved through a cascade of information from areas of the prefrontal cortex through to the primary motor cortex via the premotor system (Koechlin and Summerfield 2007; Badre and D'Esposito 2009). Anatomical evidence from humans and nonhuman primates suggests that each section of this frontal lobe hierarchy is independently connected with the cerebellum.

The architecture of the cortico-cerebellar system has been well characterized in humans and nonhuman primates. It has been suggested that the cerebellum exchanges information with the cerebral cortex within independent sets of closed cortico-cerebellar loops (Middleton and Strick 2000; Kelly and Strick 2003). Kelly and Strick (2003) have characterized 2 distinct cortico-cerebellar loops: the "motor loop" and the "prefrontal loop." In the motor loop, the primary motor cortex projects to cerebellar cortical lobules V, VI, and HVIIB and HVIII and projects back to the same regions of cortex via dorsal parts of the cerebellar dentate nucleus and the motor thalamus. In the prefrontal loop, area 46 (Walker 1940) of the prefrontal cortex projects to lobule HVIIA (mainly to Crus II and, to a lesser degree, to Crus Ip) via the pontine nuclei, and this area returns projections to the same areas of the prefrontal cortex via ventral parts of the cerebellar dentate nucleus and prefrontal thalamus (Goldman-Rakic and Porrino 1985; Barbas et al. 1991; Middleton and Strick 2001; Kelly and

Strick 2003). Connectivity studies in both humans and nonhuman primates have also demonstrated that prefrontal projections to the cerebellum originate from a range of prefrontal territories including regions as anterior as area 10 (Schmahmann and Pandya 1997; Ramnani et al. 2006; Habas et al. 2009; Krienen and Buckner 2009; O'Reilly et al. 2010; Buckner et al. 2011). The existence of connections between rostral portions of the prefrontal cortex and the cerebellum suggests that the cerebellum can automate processing within any cortical region and it is not restricted to rules that specify a motor response.

Unfortunately, there are few clear examples from functional neuroimaging that have found cerebellar activations to increasingly abstract stimuli. While previous studies have shown cerebellar activations related to complex cognitive paradigms such as language (Chen and Desmond 2005a, 2005b; Desmond et al. 2005; Kirschen et al. 2005), playing chess (Atherton et al. 2003; Chen et al. 2003), pegboard puzzles (Kim et al. 1994), and mathematical reasoning [Paced Auditory Serial Addition Task (PASAT); Hayter et al. 2007], these studies were not able to isolate confounding motor responses from cognitive elements of the task. In previous studies (Ramnani and Miall 2003, 2004; Balsters and Ramnani 2008, 2011), we have used conditional motor learning as a method for investigating the acquisition and retrieval of first-order rules without the contaminating effects of the subsequent motor response or feedback. Using this paradigm, we previously demonstrated that regions of the cerebellum interconnected with the prefrontal cortex (Crus I) were active during the acquisition and retrieval of first-order rules (Balsters and Ramnani 2008, 2011). We have previously interpreted these results as evidence that the cerebellum contributes to cognitive control, given that these activations were temporally independent of the subsequent motor processes. However, one caveat to this interpretation is that while the instruction cue is temporally independent of subsequent motor responses, the first-order rule is still linking an arbitrary stimulus with a specific motor effector and as such it is a rule that guides movement. It may be the case that the cerebellum will only process rule-related information where rules specify actions.

This study attempts to address the extent to which the cerebellum processes abstract information originating from the prefrontal cortex using functional magnetic resonance imaging (fMRI). We aim to distinguish between 2 competing hypotheses: the first is that activity within prefrontal-projecting cerebellar lobules will only be evoked by rules that specify action (i.e. first-order rules). The second hypothesis is that activity within prefrontal-projecting cerebellar lobules will be evoked by both rules that specify action and rules that specify another rule (i.e. second-order rules). In our experiment, these second-order rules were devoid of motor information and could only guide the choice of a first-order rule.

Materials and Methods

Participants

Fifteen young (18–30; 9 male) neurologically normal, right-handed subjects participated in this study. Participants gave written informed consent prior to the study, which was approved by the Trinity College Dublin School of Psychology Ethics Committee.

Trial Structure

Subjects were required to execute a delayed-response task (Fig. 1). The same basic trial structure was applied under all conditions, with condition-specific variations explained subsequently. The trial began with the presentation of an instruction cue (500 ms) that signaled which response subjects were required to make. After a variable delay period, subjects saw a "Go!" signal (250 ms) immediately followed by

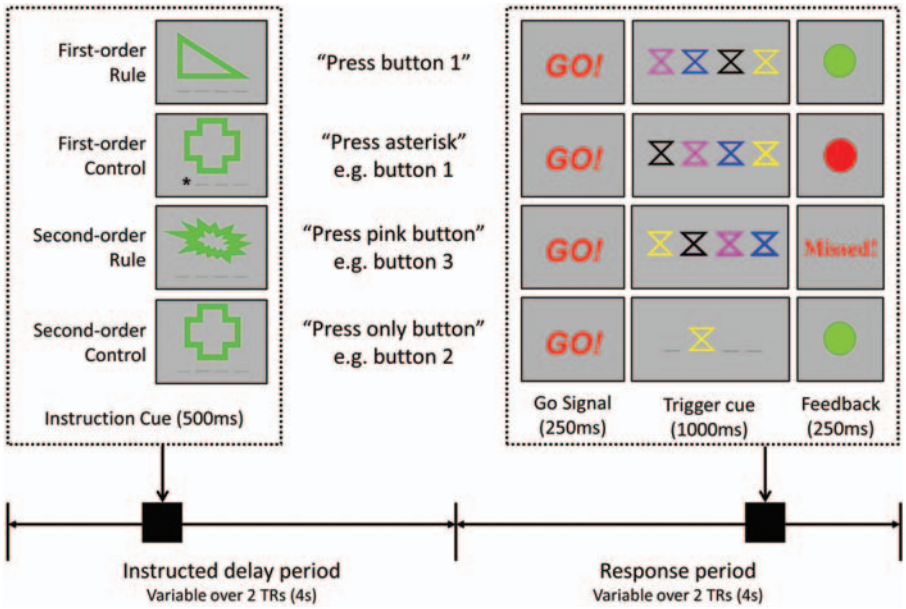

Figure 1. Trial structure: each trial was divided into two 4 s periods: the instructed delay period (0–4 s onset latency) contained the instruction cue (green shape with 4 underscores underneath, one of these underscores was replaced with an asterisk for first-order control instruction cues) and the response period (4–8 s onset latency) contained the Go! signal, immediately followed by the trigger cue where the subject made a response (pressing 1 of the 4 buttons) and feedback (green dot for correct response, red dot for incorrect, and missed for no response within the 1000 ms time window). Between each instruction cue and the trigger-related cues is the appropriate response in quotation marks. This information was not presented to subjects.

Table 1
Four conditions embedded in the 2 × 2 factorial design

	Factor 1: rule	
	Rule	Control
Factor 2: rule order		
First	First-order rule (48 trials)	First-order control (48 trials)
Second	Second-order rule (48 trials)	Second-order control (48 trials)

4 adjacent "hourglass" stimuli of different colors (1000 ms), prompting subjects to execute a response (pressing 1 of the 4 buttons on a response pad held in the right hand). The response was immediately followed by error feedback (a green dot after a correct response and a red dot after an incorrect response; 250 ms). If participants failed to execute a response within a 1000 ms time window, the word "Missed" was displayed instead of these feedback cues.

Conditions

The 4 trial types were embedded in a 2 × 2 factorial design (2 factors, each with 2 levels: Table 1). This experimental design allowed us to compare first- and second-order rules each with their own control conditions.

Factor 1: rule (rule and control): instructions either required the participant to recall an arbitrary association between the cue and the response (rule) or the instruction informed responses directly (control).

Factor 2: rule order (first-order and second-order): as well as either being a rule or control, the instruction could be either first-order or second-order. First-order instruction cues held all the information necessary for a response at the time of the instruction cue. Second-order instruction cues did not contain enough information for the participant to respond correctly, and the participant would only be able to perform the correct response after viewing the trigger cue.

This 2 × 2 factorial design resulted in 4 condition types (Fig. 1).

Condition 1: first-order rule (1stR): instruction cues consisted of a green triangle, hexagon, "bridge," and 3-quarter circle against a gray background. Underneath each shape, there were 4 adjacent underscores. Each shape had a conditional association with a specific response (pressing button 1, 2, 3, and 4, respectively). Associations between instruction cues and motor responses were acquired during pretraining immediately prior to scanning (see "Pretraining"). This stimulus type has been previously shown to evoke activity within prefrontal-projecting regions of the cerebellum (Balsters and Ramnani 2008, 2011).

Condition 2: first-order control (1stC): instruction cues consisted of a simple outlined symmetrical cross. One of the 4 adjacent underscores underneath the cross was replaced with an asterisk signaling the required response.

Condition 3: second-order rule (2ndR): instruction cues consisted of a circle, s-like squiggle, square, and "explosion." Underneath each shape were 4 adjacent underscores. Each instruction cue had a conditional association with a color (pink, blue, yellow, or black) just as each instruction cue within condition 1 (first-order rule) had a conditional association with a motor response. The instruction cue told the subject which color to match at the point of the trigger cue. For example, if the instruction cue was a circle, the participant would have to press a button which corresponded spatially to the pink trigger element. The position of each color stimulus at the point of the trigger cue would change from trial to trial, making it impossible for subjects to prepare the appropriate response prior to the presentation of the trigger cue. As with condition 1, associations between instruction cues and colors were acquired during pretraining immediately before scanning.

Condition 4: second-order control (2ndC): this instruction cue used the same image as condition 2. However, all 4 adjacent underscores were presented under the image, and thus subjects were not able to prepare a response at the time of the instruction cue. The required response was specified by the trigger cue (only 1 shape would be present at the trigger cue).

Pretraining

Before participants entered the scanner, they were informed of the stimulus associations and practiced the task for approximately 11 min (approximately 14 trials of each condition and about 3.5 presentations of each instruction cue), in order to learn all the stimulus associations. All participants were able to explicitly describe these associations before entering the scanner. Participants briefly rehearsed the task once more during the structural scan in order to confirm that they understood the task.

Experimental Timing

An important feature of this study was the ability to time-lock activity specifically to instruction cues. A variable delay was introduced between the instruction cue and the Go! signal. As in previous studies (Balsters and Ramnani 2008, 2011), this allowed us to isolate blood oxygen level-dependent (BOLD) activity time-locked to the instruction cue without the contaminating effects of subsequent trial events (Go! signal, trigger cue, motor response, and error feedback). Events in each trial took place across 4 repetition times (TRs) (0–8 s; TR = 2 s, Fig. 1). In order to optimally sample evoked hemodynamic responses (EHRs), we randomly varied the interval between scan onset and instruction cue onset over the range of the first 2 TRs from trial to trial. This achieved an effective temporal sampling resolution much finer than one TR. These intervals were uniformly distributed, ensuring that EHRs time-locked to the instruction cue were sampled evenly across the time period following each type of instruction cue. The Go! signal (along with motor responses and feedback) occurred in the period occupied by the third and fourth TR, and the timing between the third TR and its onset was varied in the same manner (in the range 4–8 s after the onset of the first TR). The range of the variable delay between the onset of instruction cues and the onset of the Go! signal varied from 832 to 6564 ms. Jittering the onset of stimuli relative to the start of each Echo Planar Imaging (EPI) volume additionally guarantees that stimuli are presented during the acquisition of every slice, and as such there is no spatial bias/neglect in our imaging protocol.

Since the instruction cues were temporally uncorrelated with the preceding and subsequent Go! signals, they could be modeled as independent event types. This allowed us to determine activity time-locked to instruction cues without the contaminating effects of the Go! signal and subsequent triggers and responses.

Functional Imaging and Analysis

Apparatus

Subjects lay supine in an MRI scanner with the fingers of their right hand positioned on a 4-button MRI-compatible response box. Stimuli were projected onto a screen behind the subject and viewed in a mirror positioned above the subject's face. Presentation software (Neurobehavioral Systems, Inc., USA) was used for stimulus presentation both inside and outside the scanner. Transistor-Transistor Logic pulses were used to drive the visual stimuli in Presentation.

Data Acquisition

A high-resolution T1-weighted anatomic magnetization-prepared rapid gradient echo image [field of view (FOV) = 230 mm, thickness = 0.9 mm, voxel size = 0.9 mm × 0.9 mm × 0.9 mm] and phase and magnitude maps were acquired first (TE_1 = 1.46 ms and TE_2 = 7 ms). Each participant then performed a single EPI session containing 782 volumes lasting 26 min. The FOV covered the whole brain, 224 mm × 224 mm (64 × 64 voxels), and 39 axial slices were acquired with a voxel size of 3.5 mm × 3.5 mm × 3.5 mm (0.3 mm slice gap), TR = 2 s, echo time = 30 ms, flip angle = 90°. All MRI data were collected on a Philips 3 T Achieva MRI Scanner (Trinity College Dublin).

Image Preprocessing

Scans were preprocessed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images were realigned and unwarped using field maps to correct for motion artifacts, susceptibility artifacts, and motion-by-susceptibility interactions (Andersson et al. 2001; Hutton et al. 2002). Images were subsequently normalized to the ICBM EPI template using the unified segmentation approach (Ashburner and Friston 2005). Lastly, a Gaussian kernel of 8 mm full width at half maximum (FWHM) was applied to spatially smooth the image in order to conform to the Gaussian assumptions of a generalized linear model (GLM) as implemented in SPM8 (Friston, Frith, Frackowiak et al. 1995; Friston, Frith, Turner et al. 1995).

Statistical Analysis

First-level single-subject analyses. Seven event types were modeled at the first level. All events were convolved with the canonical hemodynamic response function. Instruction cues for each of the 4 conditions were modeled as 4 separate event types. Trigger cues associated with first-order or second-order instructions were modeled as 2 further event types describing variance associated with the visual trigger, the motor response, and the visually presented outcome. Trials in which responses were incorrect, too early (before the trigger cue), or too late (RT > 1000 ms) were modeled separately as a seventh event type and differentiated from experimental conditions. This seventh event type included the onsets from both the instruction cue and the Go! signal in error trials. Thus, activity time-locked to incorrect trials was excluded from regressors explaining instruction-related activity. The residual effects of head motion were modeled as covariates of no interest in the analysis by including the 6 head motion parameters estimated during the realignment stage of the preprocessing. Prior to the study, a set of planned experimental timings was carefully checked so that they resulted in an estimable GLM, in which the statistical independence of the 7 event types was preserved.

Cerebellar-specific analysis (SUIT). Given that our hypotheses focussed on the cerebellum, we performed an additional analysis of the cerebellar activity using the SUIT toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm). It has been shown that normalization using SUIT produces a more accurate cerebellar normalization across participants (Diedrichsen 2006; Diedrichsen et al. 2009). Similar to the unified segmentation approach, the cerebellum and the brainstem of high-resolution T1 images were isolated (automatically generated masks were manually inspected and any nonbrain tissue removed) and warped into SUIT space. These masks were also used to isolate BOLD signal in these regions and to stop activations from overlying regions such as the visual cortex contaminating cerebellar activations. Parameters describing the nonlinear warping from individual subject space to SUIT space were later applied to first-level contrast images. These contrast images were generated using the same GLMs described earlier; however, these GLMs were run on data that were realigned and unwarped only. Contrast images were warped into SUIT space and smoothed (8 mm FWHM). In order to prevent smoothing from falsely extending cerebellar activation clusters into adjacent structures outside the cerebellum, we applied implicit masking during the smoothing preprocessing step. This effectively preserves the boundaries of the image by masking voxel values of 0 or Not a Number.

Second-level random-effects group analysis. To determine voxels significant at the group level, *t*-contrasts were incorporated into a random-effects analysis (1- or 2-sample *t*-tests). One-sample *t*-tests were used to investigate single contrast images that define main effects or interactions, for example, modeling the main effect of rule at the single-subject level (1stR + 2ndR <> 1stC + 2ndC). This contrast compares the average activity of rule cues with the average activity of control cues. This approach is commonly used in factorial designs, but may not be sufficiently stringent because a significant effect could emerge from a significant difference between only one cue compared with control cues. Two-sample *t*-tests were used to perform a conjunction analysis (Price and Friston 1997; Friston et al. 2005). A conjunction analysis is a more stringent comparison as it requires that both rule conditions must be significantly different from their respective control conditions (1stR<>1stC && 2ndR<>2ndC).

Given our anatomically specific hypothesis, a small volume correction was used (bilateral Crus I and Crus II gray matter mask) to correct for multiple comparisons. A whole cerebellar gray matter mask was also used for small volume correction (results reported in Supplementary Material). These masks were generated using the atlas of Diedrichsen et al. (2009). SPMs were thresholded at $P < 0.001$ uncorrected for display purposes, and all results reported survived a correction for multiple comparisons, either False Discovery Rate (FDR) $P < 0.05$ or small volume correction over Crus I and II.

Localization

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the T1 canonical single-subject image from the Montreal Neurological Institute (MNI) series. Results were checked against normalized T1 images of each subject. The atlas of Duvernoy and Bourgouin (1999) was used as a general neuroanatomical reference. The atlases of Schmahmann et al. (2000) and Diedrichsen et al. (2009) were employed as a specific neuroanatomical reference for cerebellar activations. We used the nomenclature of Schmahmann et al. (2000) to label cerebellar lobules. The SPM anatomy toolbox (Eickhoff et al. 2005) was used to establish cytoarchitectonic probabilities where applicable.

Results

Behavior

Error Rates

Participants' error rates were very low due to pretraining, typically 5.5% across all conditions (mean 6.53, SD 4.78 trials) with less than 2 error trials per condition (1stR: mean 1.27, SD 1.39 trials; 1stC: mean 2.2, SD 2.24 trials; 2ndR: mean 1.87, SD 1.55 trials; 2ndC: mean 1.2, SD 1.32 trials). There was no significant main effect of Factor 1: rule ($F_{1,14} = 0.17$, $P = 0.69$) or Factor 2: rule order ($F_{1,14} = 0.293$, $P = 0.6$). There was a significant interaction ($F_{1,14} = 10.03$, $P < 0.01$) driven by significant differences in the error rate between 1stR and 1stC ($P = 0.025$).

Reaction Times

Participants were significantly faster at responding to first-order (mean 334.72 ms, SD 49.61 ms) compared with second-order (mean 516.44 ms, SD 42.31 ms) instruction cues (main effect of Factor 2: rule order, $F_{1,14} = 379.01$, $P < 0.001$). Given that first-order instruction cues contained all the information necessary to respond, it is likely that participants were preparing responses when possible during the instructed delay. There was no main effect of rules on reaction time [$F_{1,14} = 1.07$, $P = 0.32$; rules (mean 427.68 ms, SD 43.65 ms) and control (mean 423.48 ms, SD 48.27 ms)] and no significant interaction between rules and rule order ($F_{1,14} = 1.34$, $P = 0.27$; 1stR: mean 334.04 ms, SD 46.05 ms; 1stC: mean 335.4 ms, SD 53.17 ms; 2ndR: mean 521.33 ms, SD 41.25 ms; 2ndC: mean 511.55 ms, SD 43.36 ms). A figure plotting condition-specific reaction times is available in Supplementary Material.

Functional Imaging

Trigger-Related Activity

Sensory and motor areas were active at the time of the trigger cue. This included right inferior frontal gyrus, middle cingulate

cortex, bilateral postcentral gyrus (including primary motor and somatosensory cortices), left inferior parietal lobule, and temporal and occipital regions. The largest activations (both in cluster size and in *t*-value) were in ipsilateral motor lobules of the cerebellum (lobules HVI and HVIIIb).

First-order versus second-order trigger activity. First-order triggers were modeled separately from second-order triggers, given the differences in reaction times between these 2 trial types. Significantly greater activity was present for second-order triggers in the primary visual regions, left supramarginal gyrus, right postcentral gyrus, right middle cingulate cortex, and left hippocampus. Motor lobules of the left and right cerebellum (lobule HVIIIb) were also significantly active. There were no significant activations where first-order triggers were greater than second-order triggers.

Instruction-Related Activity

Main effect of rule. A conjunction analysis was used to localise common areas of activity across the two contrasts: (first-order rules <> first-order control) && (second-order rules <> second-order control). The conjunction analysis showed regions of significant activation commonly seen in studies of cognitive control [left inferior frontal gyrus (pars triangularis) and left inferior parietal lobule; Cabeza and Nyberg 2000] to be more active during rule-based processing. When the main effect of rule was modeled at the first level, the same regions were also active, as well as visual regions (left fusiform gyrus, left middle occipital gyrus, right middle temporal gyrus, and right cuneus), the left superior medial gyrus (area 32), and left hippocampus. The right hemisphere prefrontal-projecting lobule Crus I was also found to be significantly more active during rule processing compared with control conditions (Table 2).

Cerebellar activations found using SUIT normalization overlapped with the results using whole-brain analysis (Supplementary Material). However, these results were now more clearly within Crus I (56% and 100% probability of being in Crus I compared with 34% using whole-brain approach), and an additional activation was present in right hemisphere Crus II. In addition, the dominant activation with Crus I now passed the significance threshold in the more stringent conjunction analysis, further suggesting that this activation was evoked by the rule-based content present in both rule instruction cues (Fig. 2 and Table 3). A comparison between activation maps using the unified segmentation approach and SUIT is available in Supplementary Material. This result exclusively supports the second of our two hypotheses that the cerebellum processes prefrontal activity regardless of whether it contains any motor information.

First-order rule versus control. A large number of regions were more active for first-order rule compared with first-order control. A number of these regions were also seen in the main effects of rules contrast described earlier. These included the left inferior frontal gyrus (pars triangularis), the left inferior parietal lobule, bilateral caudate nucleus, and medial cortical regions (middle and posterior cingulate cortices and precuneus). A small volume correction for prefrontal-projecting cerebellar lobules found a significant cluster in right Crus II specific to first-order rule compared with first-order control. This cerebellar activation cluster is spatially separate from the previously mentioned cerebellar cluster found in the whole-brain analysis (Table 2). Our SUIT analysis showed

Table 2
Main effect of rule cues (1stR + 2ndR <> 1stC + 2ndC): activity time-locked to instruction cues, FDR-corrected for multiple comparisons ($P < 0.05$) in a random-effects analysis

Rules <> controls (1stR + 2ndR <> 1stC + 2ndC)	Cluster	*T*-value	*Z*-value	Coordinates	Cytoarchitectonic BA (probability, if available)	Most active condition
Left inferior frontal gyrus (pars triangularis)	**1543**	**7.54**	**4.69**	**−46, 22, 20**	**Area 45 (40%), area 44 (30%)**	**Rules**
Left superior medial gyrus	470	6.06	4.18	−8, 20, 42	Area 32	Rules
Left inferior parietal lobule	**2037**	**7.39**	**4.65**	**−36, −50, 42**	**hIP1 (40%), hIP3 (40%)**	**Rules**
Left fusiform gyrus	477	6.56	4.36	−46, −60, −18	Area 37	Rules
Left middle occipital gyrus	669	9.38	5.2	−16, −92, −6	hOC3v (V3v) (60%), area 18 (30%), area 17 (20%)	Rules
Right cuneus	657	8.95	5.09	20, −98, 10	Area 18 (40%), area 17 (40%)	Rules
Left hippocampus	180	6.16	4.22	−26, −26, −12	Hipp (FD) (80%) and Hipp (SUB) (50%)	Rules
Right cerebellar hemisphere	991	8.14	4.87	30, −60, −34	Crus I (34%)	Rules
Right middle temporal gyrus	224	6.53	4.35	52, −70, 22	IPC (PGp) (60%)	Control
1stR <> 1stC						
Left inferior frontal gyrus (pars triangularis)	643	7.65	4.72	−46, 28, 14	Area 45 (40%)	1stR
Left middle cingulate cortex	304	6.38	4.3	−6, 4, 42	Area 6 (10%)	1stR
Left posterior cingulate cortex	631	7.35	4.63	−4, −32, 26	Area 23	1stR
Left inferior parietal lobule	420	6.32	4.28	−38, −56, 40	hIP1 (50%)	1stR
Right precuneus	173	4.81	3.63	8, −68, 42	SPL (7A) (20%)	1stR
Left caudate nucleus	104	5.3	3.85	−12, 2, 12	n/a	1stR
Right caudate nucleus	236	6.33	4.28	10, 2, 0	n/a	1stR
Right cerebellum	44	4.87	3.67	26, −78, −50	Crus II (70%)	1stR
Right middle temporal gyrus	245	6.46	4.33	54, −66, 16	IPC (PGp) (50%)	1stC
Left lingual gyrus	302	5.45	3.93	−18, −82, −16	hOC3v (30%), hOC4v (40%)	1stC
2ndR <> 2ndC						
Left inferior frontal gyrus (pars triangularis)	156	5.33	3.88	−46, 26, 14	Area 45 (50%)	2ndR
Left posterior cingulate cortex	239	5.02	3.74	−2, −32, 32	Area 23	2ndR
Left precentral gyrus	724	5.97	4.14	−52, 0, 36	Area 6 (10%)	2ndR
Left lingual gyrus	10 876	9.3	5.18	−14, −88, −12	hOC3v (60%), area 18 (40%)	2ndR
Left hippocampus	394	5.27	3.85	−24, −26, −10	Hipp (SUB) (30%), (FD) (20%)	2ndR
Right cerebellum	1205	5.54	3.97	30, −60, 32	HVI (81%), Crus I (19%)	2ndR
Right cerebellum	45	4.22	3.68	10, −84, −38	Crus II (84%)	2ndR

Note: Cluster size indicates the number of voxels active in each cluster. *X*-coordinates with a negative value represent activity in the left hemisphere. Activations highlighted in bold were also present in more stringent conjunction analysis (1stR<>1stC && 2ndR<>2ndC; $P < 0.05$, FDR-corrected). The final column indicates the most active condition, that is, "Rules" indicates that rule cues (1stR + 2ndR) were more active than control cues (1stC + 2ndC). 1stR, first-order rule; 1stC, first-order control; 2ndR, second-order rule; 2ndC, second-order control.

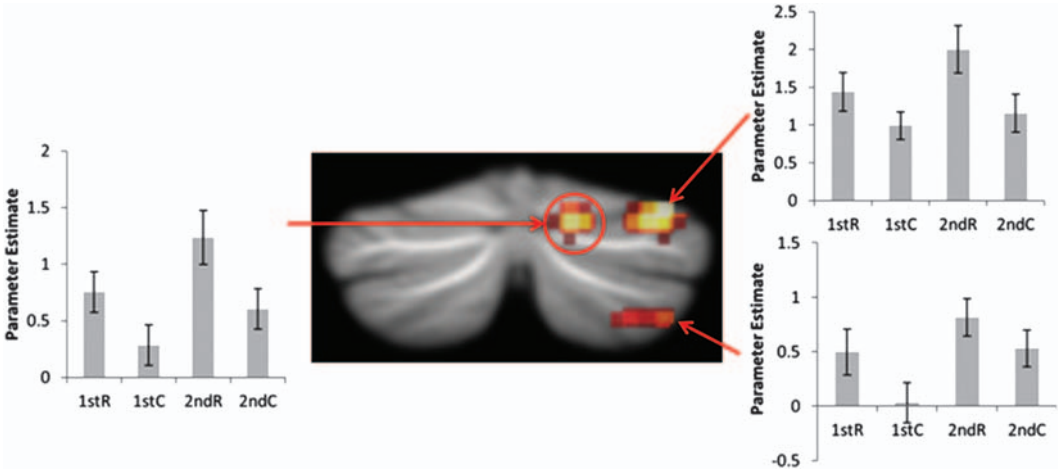

Figure 2. Cerebellar activations for main effect of rule: activation for rule instruction cues greater than control instruction cues within the right hemisphere Crus I and Crus II overlayed on SUIT template. Left and right of the activations are plots of parameter estimates for medial Crus I, lateral Crus I, and lateral Crus II (arrows indicate which plots correspond to which activation). Activation in medial Crus I (circled) additionally survived a more stringent conjunction analysis of main effect of rules.

Table 3
Main effect of rule cues (1stR + 2ndR <> 1stC + 2ndC) using SUIT normalization: activity time-locked to instruction cues, small volume corrected using a Crus I and Crus II mask

Rules <> controls (1stR + 2ndR <> 1stC + 2ndC)	Cluster	*T*-value	*Z*-value	Coordinates	Cerebellar lobule (probability, if available)	Most active condition
Right cerebellum, Crus I	**390**	**6.03**	**4.17**	**16, −76, −27**	**Crus I (56%)**	**Rules**
Right cerebellum, Crus I	Same cluster	6.03	4.17	34, −74, −25	Crus I (100%)	Rules
Right cerebellum, Crus II	43	4.75	3.61	28, −78, −53	Crus II (55%)	Rules
1stR <> 1stC						
Right cerebellum, Crus I	10	5.36	3.89	44, −66, −33	Crus I (99%)	1stR
Left cerebellum, Crus I	12	4.56	3.51	28, −84, −55	Crus II (46%)	1stR
2ndR <> 2ndC						
Right cerebellum, Crus I	15	5.39	3.9	44, −42, −33	Crus I (48%)	2ndR
Right cerebellum, Crus I	125	4.69	3.58	34, −66, −29	Crus I (99%)	2ndR
Right cerebellum, Crus I	24	4.36	3.41	12, −78, −23	Crus I (71%)	2ndR
1stR <> 2ndR						
Left cerebellum, Crus I	223	8.01	4.83	−46, −68, −31	Crus I (100%)	2ndR
Right cerebellum, Crus I	38	4.48	3.47	32, −64, −31	Crus I (79%)	2ndR
Left cerebellum, Crus I	15	4.25	3.35	−32, −82, −25	Crus I (62%)	2ndR
Right cerebellum, Crus I	22	4.14	3.29	8, −80, −25	Crus I (78%)	2ndR

Note: Cluster size indicates the number of voxels active in each cluster. Coordinates are in SUIT space, which is similar but not identical to the MNI space. *X*-coordinates with a negative value represent activity in the left hemisphere. Activations highlighted in bold were also present in more stringent conjunction analysis (1stR<>1stC && 2ndR<>2ndC; $P < 0.05$, FDR-corrected). The final column indicates the most active condition, that is, Rules indicates that rule cues (1stR + 2ndR) were more active than control cues (1stC + 2ndC). 1stR, first-order rule; 1stC, first-order control; 2ndR, second-order rule; 2ndC, second-order control.

activations in medial Crus I and lateral Crus II, which overlapped with the activation described earlier (SUIT analysis of main effect of rules). We also note that the Crus II activation mentioned earlier in the whole brain and SUIT analyses overlaps with the Crus II activation found in the SUIT main effect of rules analysis (Table 3).

Second-order rule versus control. Significantly greater activity for second-order rules compared with controls was found in the visual cortex, left inferior frontal gyrus (pars triangularis), left precentral gyrus, left posterior cingulate cortex, and left hippocampus. A small volume correction for prefrontal-projecting cerebellar clusters showed 2 significant cerebellar activations: the first was in the right cerebellar lobule Crus I and overlapped with the cerebellar activation described in the main effects of rule contrast. The second activation was in the right cerebellar lobule Crus II. This cluster is spatially separate from the 2 whole-brain cerebellar activations mentioned earlier (Table 2). As in the whole-brain analysis, our SUIT analysis showed activation in the right cerebellar lobule Crus I overlapping with the activation described in the main effects of rule contrast. This activation is now more certainly in Crus I (99%), compared with the activation found in the whole-brain analysis (19%) (Table 3).

Main effect of rule order. A conjunction analysis was also used to compare (first-order rules <> second-order rules) && (first-order control <> second-order control). Only one significant difference was found within the left supramarginal gyrus, extending to the postcentral gyrus. When rule order was modeled at the first level, additional significant clusters were found, including the left and right precentral gyri (area 4a and area 4p, respectively), the left middle and right superior orbital gyri (area 11), and the left insula. An activation cluster was also present in the right hemisphere motor-projecting cerebellar lobule HVI (90%) (Table 4). The

Table 4

Main effect of rule order (1stR + 1stC <> 2ndR + 2ndC): activity time-locked to instruction cues, FDR-corrected for multiple comparisons ($P < 0.05$) in a random-effects analysis

First-order <> second-order (1stR + 1stC <> 2ndR + 2ndC)	Cluster	*T*-value	*Z*-value	Coordinates	Cytoarchitectonic BA (probability, if available)	Most active condition
Left insula lobe	150	5.87	4.1	−38, −4, 12	OP3 (20%)	First order
Left postcentral Gyrus/supramarginal gyrus	1111	6.03	4.17	−58, −24, 40	IPC (PFt) (50%), area 2 (50%)	First order
Right superior orbital gyrus	147	5.06	3.75	24, 38, −14	Area 11	Second order
Left middle orbital gyrus	156	6.39	4.3	−24, 40, −10	Area 11	Second order
Left precentral gyrus	148	3.94	3.18	−42, −6, 34	Area 4p (20%)	Second order
Right precentral gyrus	231	6.35	4.29	42, −10, 40	Area 4a (40%)	Second order
1stR <> 2ndR						
Right inferior frontal gyrus (pars opercularis)	140	6.32	4.28	56, 8, 12	Area 44 (60%)	1stR
Left insula	180	7.94	4.81	−38, −4, 12	Op 3 (20%)	1stR
Right supramarginal gyrus	415	6.44	4.32	58, −26, 42	IPC (PFt) (50%)	1stR
Left supramarginal gyrus	815	5.9	4.11	−56, −30, 38	IPC (PFt) (50%)	1stR
Left inferior frontal gyrus (pars triangularis)	503	6.93	4.49	−44, −6, 34	Area 44 (30%)	2ndR
Right inferior frontal gyrus (pars orbitalis)	238	5.94	4.13	36, 28, −6	Area 47	2ndR
Left lingual gyrus	2599	6.74	4.43	−20, −70, −2	hOC3v (40%)	2ndR

Note: Cluster size indicates the number of voxels active in each cluster. *X*-coordinates with a negative value represent activity in the left hemisphere. Activations highlighted in bold were also present in more stringent conjunction analysis (1stR<>2ndR && 1stC<>2ndC; $P < 0.05$, FDR-corrected). The final column indicates the most active condition, that is, "First order" indicates that first-order cues (1stR + 1stC) were more active than second-order cues (2ndR + 2ndC). 1stR, first-order rule; 1stC, first-order control; 2ndR, second-order rule; 2ndC, second-order control.

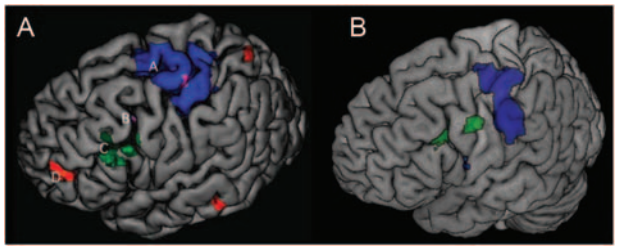

Figure 3. (*A*) Image from Badre and D'Esposito (2007) showing frontal lobe hierarchy. Superimposed on this figure: A (blue) refers to first-order rules, B (purple) refers to second-order rules, C (green) refers to third-order rules, and D (red) refers to fourth-order rules. (*B*) Results from this study showing first-order rules > second-order rules (blue) and second-order rules > first-order rules (green).

SUIT analysis showed no significant differences in the cerebellum.

First-order rule versus second-order rule. First-order rules evoked significantly greater activations in the right inferior frontal gyrus (pars opercularis), left insula, and bilateral supramarginal gyrus. Second-order rules evoked significantly greater activations in a different portion of the right inferior frontal gyrus (pars orbitalis), as well as left inferior frontal gyrus (par triangularis), and visual cortex. When comparing these activations, it is clear to see that second-order rules were processed in more anterior regions of the prefrontal cortex compared with first-order rules (Fig. 3). This is in keeping with theories of a rostrocaudal functional gradient within the prefrontal cortex and mirrors the results of other studies (Koechlin and Summerfield 2007; Badre and D'Esposito 2009). There were no significant differences between first- and second-order rules in the cerebellum (Table 4).

While the whole-brain analysis did not find any significant differences in the cerebellum for first- versus second-order rules, our SUIT analysis showed a number of significant cerebellar activations. This included activations in left and right cerebellar lobules Crus I and Crus II. Activation was also present in vermal lobule VI for first-order rules > second-order rules, most likely reflecting the difference in motor preparation at the time of the instruction cue (Table 3). A figure illustrating the activation and parameter estimates for each condition is presented in Supplementary Material.

Interaction. The only region showing a significant interaction was the primary visual cortex. Activity in this region was greatest for second-order rules. Neither whole-brain nor SUIT analyses showed any significant interactions within the cerebellum. Given that there were no significant interactions within prefrontal-projecting cerebellar lobules, our first hypothesis (activity within prefrontal-projecting cerebellar lobules will only be evoked by rules that specify action) was not supported.

Discussion

In this study, we investigated whether the cerebellum responds only when rules specify the properties of action or whether the cerebellum additionally processes rules relating to cognitive control independent of such action properties. We focussed our analysis on activity time-locked to the instruction cue, thus isolating cognitive processes specifically related to rule-based processing (translation of symbolic information into additional rules or actions) and removing additional confounding processes (i.e. motor responses and processing of feedback). Our results support the hypothesis that prefrontal-projecting cerebellar lobules (Crus I and Crus II) process rule-based information, regardless of whether or not rules specify actions.

Differences in Processing First- and Second-Order Rules in the Frontal Lobes

While a number of studies have proposed a rostrocaudal functional hierarchy in the frontal lobes (Koechlin et al. 2003; Badre and D'Esposito 2007, 2009; Koechlin and Summerfield 2007; Badre et al. 2009, 2010; Race et al. 2010), there are other studies that suggest that cytoarchitectonic subdivisions of the prefrontal cortex do not necessarily lead to functional subdivisions (Duncan and Owen 2000; Duncan 2001; Rowe et al. 2008). The adaptive coding model of the prefrontal cortex (Duncan 2001) suggests that any region of the prefrontal cortex is capable of integrating nearly any kind of information due to the extremely plastic nature of prefrontal

neurons. Examples of this can be seen from electrophysiological recordings of the primate prefrontal cortex (Rao et al. 1997; Freedman et al. 2001) and functional neuroimaging (Duncan and Owen 2000; Rowe et al. 2008). Both Badre and D'Esposito (2007) and Rowe et al. (2008) compared dimensions of cognitive control with task competition using fMRI and arrived at different results. The work of Badre and D'Esposito (2007) showed a rostrocaudal hierarchy of cognitive control with increasingly abstract stimuli activating increasingly anterior regions of the prefrontal cortex. However, Rowe et al. (2008) specifically compared action selection (the choice between action alternatives in the absence of a specified rule) with rule selection (deciding to respond using either height or brightness as a rule compared with being specified to use highest, lowest, lightest, or darkest) and found a spatial overlap in the prefrontal cortex rather than a hierarchy of prefrontal regions. The results of our study are comparable with the results of Badre and D'Esposito (2007) along with other studies (Koechlin et al. 2003; Badre et al. 2010; Race et al. 2010), showing more anterior prefrontal activations for second-order compared with first-order rules (Fig. 3). The spatial overlap between the results of Badre and D'Esposito (2007) and this study is presented in Figure 3. First-order rules appear to activate more dorsal and caudal regions of the frontal lobe, whereas second-order rules appear to activate more rostral and ventral portions of the prefrontal cortex, most likely pre-PMd as seen in other studies (Badre and D'Esposito 2007; Badre et al. 2010). Rowe et al. (2008) suggest that differences between their results and the results of Koechlin et al. (2003) and Badre and D'Esposito (2007) may be due to differences in the experimental design. Koechlin et al. (2003) used a block design, whereas Badre and D'Esposito (2007) had an event-related design, and the levels of task abstraction (cognitive complexity) were kept constant during fMRI sessions. Rowe et al. (2008) presented all trial types pseudo-randomly within a single fMRI session. However, we also included all trial types pseudo-randomly intermixed within a single fMRI session and found a result similar to that of Badre and D'Esposito (2007). It may be the case that the additional temporal jittering of instruction cues removed some of the noise of subsequent cognitive and motor confounds and increased the signal of cognitive processes of interest, thus giving us results different from Rowe et al. (2008). It is also possible that the temporal jittering improved the temporal resolution of our fMRI response (Josephs and Henson 1999), perhaps enough to detect temporal as well as spatial dynamics of the prefrontal hierarchy (Koechlin and Summerfield 2007; Race et al. 2010).

Differences in Processing First- and Second-Order Rules in the Cerebellar Cortex

In a previous study (Balsters and Ramnani 2008), we used an identical conditional motor task comparing symbolic and direct instruction cues that could be used to prepare an action and found an activation cluster specific to symbolic instruction cues (identical to first-order rule stimuli in this study) within right hemisphere Crus I. The activation cluster found in Balsters and Ramnani (2008) is spatially consistent with the cluster presented in Figure 2, replicating our previous results that prefrontal-projecting cerebellar lobule Crus I is involved in processing first-order rules. Given that this cluster was also active for the processing of second-order rules, we can further suggest that this activation is not due to the integration of motor effectors and sensory cues, but rather relates to the abstract translation of a sensory stimulus into a future response, even when that future response is another rule and not a motor response.

Activity within left inferior frontal gyrus (pars triangularis) and right cerebellar lobule Crus I has been found in studies of language and verbal working memory (Kirschen et al. 2005; Stoodley and Schmahmann 2009). However, we would argue that processes that engage these brain regions are not restricted to verbal working memory, but a wide range of processes that includes the acquisition of rules. Lesion studies have repeatedly shown that rule learning, and the implementation of previously learned rules, is severely impaired after lesions to the ventrolateral prefrontal cortex (Murray et al. 2000; Passingham et al. 2000; Bussey et al. 2002). Similarly, a number of neuroimaging studies have shown activations in the inferior frontal gyrus during conditional motor learning (Toni and Passingham 1999; Toni, Ramnani et al. 2001; Toni, Rushworth et al. 2001; Bunge et al. 2003; Brass and von Cramon 2004). Given that our experimental design matched requirements for verbal working memory under experimental and control conditions, our results are consistent with the interpretation that the effects are related to rule-based information processing rather than verbal working memory.

As hypothesized, rule-based processes occurring at the presentation of a symbolic cue elicited activity within prefrontal-projecting cerebellar lobules (primarily Crus I but also Crus II). It is important to reiterate that while Kelly and Strick (2003) showed that connections with Crus II were more abundant than those with Crus I, both clearly have access to information from the prefrontal cortex. Other studies have investigated monosynaptic connections from prefrontal cortical regions to the pontine nuclei (Schmahmann and Pandya 1997), but to our knowledge, no other tracer study has investigated the topography of anatomical connections between the prefrontal cortex and the cerebellar cortex in greater detail than that of Kelly and Strick (2003). However, there are increasingly detailed studies investigating cortico-cerebellar connectivity in humans using resting-state fMRI (Habas et al. 2009; Krienen and Buckner 2009; O'Reilly et al. 2010; Buckner et al. 2011). These studies mostly provide support for the view that the system is similarly organized in the human brain compared with the nonhuman primates. Krienen and Buckner (2009) and O'Reilly et al. (2010) recently reported that resting-state activity in Crus II could be explained by fluctuations in resting-state activity in the dorsolateral prefrontal cortex, consistent with the findings of Kelly and Strick (2003) in capuchin monkeys. Interestingly, Krienen and Buckner (2009) showed that activity within parts of Crus I and Crus II covaried with the dorsolateral prefrontal cortex, but, in addition, there are adjacent areas of Crus I in which activity corresponds to medial portions of the prefrontal cortex. Our main effect of rules activated regions in the inferior frontal gyrus (area 45), which Schmahmann and Pandya (1997) have shown send projections to the pontine nuclei. Similarly, Ramnani et al. (2004) have demonstrated that fiber pathways in humans originating in the inferior frontal gyrus pass through the anterior segments of the cerebral peduncle before penetrating the pons. In addition to structural evidence, Buckner et al. (2011) provide functional

evidence that resting fluctuations within ventral portions of the prefrontal cortex covary with resting fluctuations in the cerebellar lobule Crus I. The frontal and cerebellar activations reported in Buckner et al. (2011) appear to spatially overlap with the results of this study, and it is likely that rule-based processing activates this cortico-cerebellar circuit.

It has been suggested that eye movements explain much of the cerebellar activity associated with cognitive tasks in neuroimaging experiments and that these areas are connected with the frontal eye fields (Glickstein and Doron 2008). Although the cerebellar cortex does indeed have connections with the frontal eye fields, these are in addition to a number of other prefrontal regions that connect with the cerebellum, but make no known contributions to the kinematics of eye movements. For example, Glickstein et al. (1985) have shown dense projections to the pontine nuclei from areas 24 and 25, which are well known for their involvement in decision making and the regulation of mood, respectively (Devinsky et al. 1995; Mayberg et al. 2005; Lozano et al. 2008; Hamani et al. 2009). In our study, participants had to initiate a visual search to respond to second-order instruction cues. However, there are a number of reasons why this would not impact on the results presented here. First, visual searches were made at the time of the trigger, not at the time of the instruction cue (rule-related activity was time-locked to the instruction cues, not to the trigger cues). Given that second-order instruction cues specified a response at the time of the trigger, it is possible that there may have been eye movement preparation during second-order instruction cues that was not present for first-order instruction cues. However, our comparison of interest was between rule and control instruction cues, not first- and second-order instruction cues. The eye movement demands were equal for both first-order rules compared with first-order controls and second-order rules compared to second-order controls. This is supported by the fact that we find no evidence of activity in the eye movement circuits in this study, further suggesting that activity is unlikely to be related to eye movement demands. We do not agree that cerebellar activity in neuroimaging studies can be explained purely by eye movements, partly because most studies provide adequate experimental control for this confound. There are also, for example, studies that make cognitive demands in the total absence of any visual demands (see Hayter et al. 2007, in which there were no visual demands at all; in this experiment, stimuli were auditory and responses were verbal).

One caveat to this study is that while participants could not prepare a specific effector for second-order rules, they may have been preparing a response at the level of the whole hand or multiple digits. We would argue against this interpretation, given that the contrast for main effect of rules failed to show a significant difference in reaction times or highlight any preparatory activity within the premotor cortex (a small volume correction using a cytoarchitectonic mask of area 6; Geyer 2004). However, without a direct measure of muscle movements in the hand, we cannot completely discount this possibility. Bischoff-Grethe et al. (2002) neatly disambiguate cerebellar contributions to motor control from shifts in attention using a combination of response and no-response conditions. However, conditional motor learning paradigms require the subject to make a specific response to an instruction cue. A condition without a motor response would be qualitatively different from the other conditions in this study. The differences between the experimental conditions presented in this study and this hypothetical control condition would extend well beyond motor preparation and as such would not offer improved experimental control.

This study provides strong support for the cerebellar contributions to cognitive control; however, future research should investigate cortico-cerebellar interactions during decision making. Both Ramnani (2006) and Ito (2008) have endeavored to expand cortico-cerebellar models of motor control such as those of Kawato, Miall, and Wolpert (Kawato and Wolpert 1998; Wolpert and Kawato 1998; Wolpert et al. 1998). Ramnani (2006) predicted that activity would be greatest within the frontal lobe during the formation of novel rules or motor sequences and that activity within these regions would decrease during learning (Jueptner et al. 1997; Boettiger and D'Esposito 2005). This decrease in activity within the frontal lobe would coincide with an increase in interconnected cerebellar territories, representing the acquisition and automatization of prefrontal and motor processes. This would also lead to a shift in the locus of control, such that the cerebellum would output well-rehearsed motor and prefrontal skilled processes rather than its cortical counterpart. However, this has not been supported by previous neuroimaging studies, which mostly show a decrease in cerebellar activity during learning and automaticity (Imamizu et al. 2000; Doyon et al. 2002; Penhune and Doyon 2005; Balsters and Ramnani 2011). This could relate to the decreases in complex and simple spikes seen in electrophysiology studies of the cerebellum during skill acquisition (Gilbert and Thach 1977; De Zeeuw and Yeo 2005; Medina and Lisberger 2008; Lepora et al. 2009), or it could suggest that the cerebellum is involved in adapting and tuning cortical processes but does not act as a storage for these processes (Doyon et al. 2003; Debas et al. 2010). This is an area that requires further investigation, and we would suggest that future studies investigate cortico-cerebellar connectivity (possibly using dynamic causal modeling) to try and establish how neocortical and connected cerebellar areas interact during learning (Apps et al. 2009; Saalmann et al. 2009).

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfourdjournals.org/.

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