Decreased cerebellar-cerebral connectivity contributes to complex task performance

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Katz C, Knops A. Decreased cerebellar-cerebral connectivity contributes to complex task performance. J Neurophysiol 116: 1434–1448, 2016. First published June 22, 2016; doi:10.1152/jn.00684.2015.—The cerebellum’s role in nonmotor processes is now well accepted, but cerebellar interaction with cerebral targets is not well understood. Complex cognitive tasks activate cerebellar, parietal, and frontal regions, but the effective connectivity between these regions has never been tested. To this end, we used psycho-physiological interactions (PPI) analysis to test connectivity changes of cerebellar and parietal seed regions in complex (2-digit by 1-digit multiplication, e.g., 12 × 3) vs. simple (1-digit by 1-digit multiplication, e.g., 4 × 3) task conditions (“complex — simple”). For cerebellar seed regions (lobule VI, hemisphere and vermis), we found significantly decreased cerebellar-parietal, cerebellar-cingulate, and cerebellar-frontal connectivity in complex multiplication. For parietal seed regions (PFCm, PFP, PFm) we found significantly increased parietal-parietal and parietal-frontal connectivity in complex multiplication. These results suggest that decreased cerebellar-cerebral connectivity contributes to complex task performance. Interestingly, BOLD activity contrasts revealed partially overlapping parietal areas of increased BOLD activity but decreased cerebellar-parietal PPI connectivity.

NEW & NOTEWORTHY

The cerebellum supports cognitive task performance through bidirectional task-driven connectivity with the cerebral cortex. Previous neuroimaging studies have found coactivation of cerebellar and cerebral regions when subjects performed relatively complex tasks. Here we show that cerebellar lobule VI connectivity with posterior parietal, cingulate, and frontal regions decreases with increasing task complexity. Thus increased cerebellar-cerebral connectivity in relatively simple, automated tasks and decreased connectivity in more demanding tasks may contribute to cognitive performance.

Understanding the role of the cerebellum in functional networks is a key step toward refining models, creating accurate brain maps, and possibly identifying treatment targets. Once thought to be exclusively devoted to motor processes, the cerebellum is now known to be involved in nonmotor cognitive processes (for review see Buckner 2013; Rapoport et al. 2000; Schmahmann 2010; Strick et al. 2009). Similar to its role in motor response, the cerebellum is thought to regulate cognitive processes so that they are appropriately implemented for a given task (Schmahmann 2010). Cerebellar regulation might be due to the cerebellar role in timing and sequencing (Spencer and Ivry 2013), sensorimotor imagery (Hanakawa et al. 2008; Lotze et al. 1999) including speech (Ackermann et al. 1998), and adaptive plasticity underlying learning (Wolpaw and Chen 2006). Adaptive plasticity has been extensively studied in motor learning (Gao et al. 2012; Mauk et al. 1997) but can also apply to nonmotor cognitive processes (Ito 2008) and maintenance of operantly conditioned behaviors (Wolpaw and Chen 2006). However, these roles are not mutually exclusive (Strick et al. 2009). The inappropriate implementation of behavior seen with cerebellar damage can affect both motor and cognitive processes and has been termed “dysmetria of thought” (Schmahmann 1991, 1998). This understanding of cerebellar function has improved diagnosis and treatment of neurological abnormalities such as cerebellar cognitive affective syndrome (Schmahmann and Sherman 1998). However, cognitive models frequently leave out the cerebellum, even for processes with consistent cerebellar activity. For example, in relatively complex mental calculation a meta-analysis showed cerebellar activation (Arsalidou and Taylor 2011), yet the cerebellum is not included in mental calculation models.

Cerebellar-parietal loops are hypothesized to play a role in cognitive processes (Stoodley et al. 2012). The disruption of cerebellar-parietal loops may explain the spatial, conceptual, sequential organizational, and navigational impairments in cerebellar dysfunction (Schmahmann 2010). In chronic cannabis users, abnormal parietal-cerebellar connectivity was correlated with impaired response inhibition (Behan et al. 2014). Cerebellar-parietal interactions are also consistent with the parietal lobe’s role in attention-demanding cognitive processes (Behrmann et al. 2004; Cabeza et al. 2008; Colby and Goldberg 1999). For example, during attention to motion vs. fixation, a cluster in right cerebellar lobule VIIa (CrusI) increased connectivity to dorsal visual stream regions (e.g., PPC) as well as visual regions (V5) (Kellermann et al. 2012). It remains to be seen whether this increased connectivity would persist in more cognitively demanding tasks such as working memory, mental calculation, or mental rotation. Posterior cerebellar and parietal areas are both activated by more complex working memory and visual-spatial processing tasks (Stoodley et al. 2012; Stoodley and Schmahmann 2009). However, this coactivation might not be driven by a common task-related network (i.e., effective connectivity). Although activation clusters reveal regions with task-driven local blood oxygenation level-dependent (BOLD) activity changes, connectivity changes between these clusters cannot be assumed. In other words, activity in one cluster may not be related to or dependent on activity in another cluster. To determine which regions are involved in

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a task-related network, task-based effective connectivity analysis is needed.

Although not directly addressing task-driven connectivity changes, there is evidence for cerebellar-cerebral functional networks. These networks support both motor and nonmotor processes. In humans, most of the cerebellum correlates with the cerebral association rather than somatomotor regions (Buckner et al. 2011) and has similar functional asymmetry (Lu et al. 2011; Wang et al. 2013). Potentially distinct (however, overlap remains an open question) cerebellar regions participate in known cerebral functional connectivity networks (Buckner et al. 2011; Habas et al. 2009; O’Reilly et al. 2010).

Lobule VI was part of the salience network involving left medial frontal, dorsal anterior cingulate, dorsolateral prefrontal cortex (PFC), frontoinsular, and thalamus clusters; lobule VIIa was part of the executive control network involving the PFC, orbitofrontal, superior parietal, and angular gyrus (AG) clusters (Habas et al. 2009). To date, no study has used effective connectivity analysis (i.e., task-driven seed-based functional connectivity) to examine the relationship between cerebellar seed regions and the cerebrum during complex cognitive tasks (e.g., working memory, mental rotations, mental calculation).

This has limited interpretation of cerebellar functional imaging research (resting state, BOLD, PET) (Keren-Happuch et al. 2014). Thus the exact relationship between the cerebellum and the parietal lobe during cognitive task performance remains unclear (Keren-Happuch et al. 2014; Stoodley et al. 2012).

Anatomically, there is evidence from nonhuman primates for nonmotor cerebellar-cerebral connections (Dum and Strick 2003; Strick et al. 2009). As evidenced by retrograde transneuronal tracers injected into M1, projections to motor areas (M1) account for only part (30%) of the cerebellar dentate nucleus output channels (Dum and Strick 2003; Hoover and Strick 1999). Some remaining dentate neurons are labeled by injection into parietal and frontal regions. The intraparietal sulcus (IPS) (7b), the middle frontal gyrus (BA46), and anterior intraparietal region AIP receive input from nonoverlapping dentate neurons (Clower et al. 2001; Dum and Strick 2003). Posterior parietal regions LIP and MIP receive inputs from the dentate and interpositus nucleus (Prevosto et al. 2010). A ventral dentate area innervating BA9 and BA46 is also labeled by injection into frontal region preSMA (Dum and Strick 2003; Picard and Strick 2001). These targets of cerebellar output exhibit reciprocal connections back to cerebellum through the pons, and although this has not been tested for all cerebral targets, closed-loop circuits are likely a feature of cerebellar-cerebral loops (D’Angelo and Casali 2012; Strick et al. 2009).

Functionally, there is evidence for motor and nonmotor cerebellar regions. Generally, lobules VI and VII, as well as IX, are thought to specialize in cognitive tasks, whereas lobules I–V and VIII are thought to specialize in sensory-motor tasks (Schmahmann 2000), although research into the roles of various regions is ongoing (Buckner et al. 2011; Diedrichsen and Zotow 2015). Lobules VI and VII are involved in attention, working memory, and spatial processing (Baier et al. 2009, 2010; Broussard 2013). For example, lobules VI and VIIa were both activated by increasing working memory load (Kirschen et al. 2005, 2010; Stoodley et al. 2012). Interestingly, lobule VI was deactivated by practice and automation during PET scanning (Raichle et al. 1994). Similarly, CrusI was also deactivated by practice, and this was specific to the rule processing rather than related actions (Balsters and Ramnani 2011). Thus lobules VI and VII seem to play an important role in complex (e.g., greater working memory load, attentional demands, mental rotation demands, novel tasks) vs. simple automated (e.g., baseline conditions, practiced tasks) tasks in multiple domains. These involvements in multiple domains make lobules VI and VII interesting seed regions for complex task networks.

Mental arithmetic tasks are ideal for studying complexity because there is clearly a correct answer (Ravizza et al. 2008). Furthermore, complexity can be increased with minimal added confounds (e.g., familiarity, visual presentation). Previous functional imaging research comparing simple to complex symbolic multiplication has shown parietal and frontal activation (Krueger et al. 2011; Zago et al. 2001) as well as cerebellar activation (Zago et al. 2001). Within single-digit multiplication problems, increasing difficulty activated SMA, anterior cingulate, and inferior frontal regions (Jost et al. 2009). We use the simple vs. complex distinction but recognize that complex tasks involve multiple-domain general cognitive processes.

In contrast to the cerebellum, the parietal lobe has been more extensively studied and shown to play a pivotal role in cognitive tasks, including mental arithmetic (Dehaene et al. 2003). Granger causality analysis has shown increased parietal-to-parietal and frontal-to-parietal connectivity for increasingly complex symbolic multiplication (Krueger et al. 2011). During nonsymbolic numerical tasks, psycho-physiological interactions (PPI) analysis showed increased parietal-parietal and parietal-frontal connectivity (Park et al. 2013). However, parietal connectivity during symbolic arithmetic has not been studied with PPI.

We hypothesized that cerebellar connectivity would change as a function of task complexity, most likely increasing for complex tasks. We also anticipated that in complex tasks inferior parietal (IPL) and IPS regions would increase connectivity with parietal, frontal, and cerebellar regions.

MATERIALS AND METHODS

We analyzed connectivity patterns during complex and simple task performance. Adult human subjects performed simple, single-digit (e.g., $4 \times 3$) and complex, multidigit (e.g., $12 \times 4$) multiplication during fMRI scanning. Cerebellar analysis focused on lobules VI and VIIa/CrusI because of their role in a variety of complex cognitive tasks. We were particularly interested in lobule VI because of its role in attentional shifts and previous findings of attentional shifts underlying mental calculation (Dormal et al. 2014; Knops et al. 2009a). Since the tasks were matched for overt motor demands (i.e., response selection) we did not expect cerebellar motor network involvement. Still, arithmetic continues to involve early finger-counting networks in educated adults (Andres et al. 2012; Tschentscher et al. 2012). However, arithmetic continues to involve early finger-counting networks in educated adults (Andres et al. 2012; Tschentscher et al. 2012). Finger-counting networks may also support multiplication (Zago et al. 2001) as well as cerebellar activation (Krueger et al. 2011). During nonsymbolic numerical tasks, psycho-physiological interactions (PPI) analysis showed increased parietal-parietal and parietal-frontal connectivity (Park et al. 2013). However, parietal connectivity during symbolic arithmetic has not been studied with PPI.

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We chose PPI analysis because it tests connectivity changes as a function of task condition. In other words, PPI analysis demonstrates functionally significant connectivity changes. This feature is similar to BOLD activity contrasts in traditional fMRI studies. In addition to PPI’s advantages in determining functional significance, PPI provides a closer match to neuronal connectivity than other connectivity analysis methods. PPI analysis of deconvolved fMRI data (Gitelman et al. 2003) was consistent with neuronal interactions (Kim and Horwitz 2008) and thus provides biologically plausible results.

In the present study, we examined connectivity changes associated with increasing complexity. Our goal was to test how the experimental manipulation (i.e., task complexity) related to changes in neural connectivity. Because PPI analysis specifically tests task-related changes, it is not necessary to first conduct traditional BOLD analysis and limit PPI analysis to areas with net BOLD activity changes. Indeed, PPI analysis may reveal areas involved in the task that are invisible on BOLD contrasts. PPI controls for the main effect of task and physiological correlation. Therefore, the task-specific connectivity change is over and above the change in correlation between two areas due to the main effect of task or nontask correlations. PPI seed region selection can be based on functional activation in BOLD contrasts, anatomical regions, or independent component analysis (ICA)-derived regions. Although also a reasonable method, BOLD contrast masks do not necessarily improve detection of regions involved in connectivity vs. localized activity. Considering this, we use easily generalizable anatomical regions that contain task-based BOLD activity. Anatomical definition is a well-accepted and commonly used method in PPI analysis (see O’Reilly et al. 2012). It should be noted that the anatomical seed region acts as a mask from which each subject’s task-related activity is extracted (see Connectivity analysis). We refer to PPI as “effective connectivity,” but it is also referred to as “functional connectivity.” We use the term “effective connectivity” because it is a model-driven, seed-based regression analysis, in contrast to model-free, temporal correlational analysis characteristic of functional connectivity. Still, it should be noted that PPI analysis is also different from other effective connectivity methods such as dynamic causal modeling (DCM), in that it does not imply causality as expressed in claims such as “region A drives region B.” In other words, although a seed region is chosen, the directionality is purely statistical and reversible. PPI does not differentiate afferent vs. efferent connectivity.

Subjects

Seventeen healthy right-handed subjects (20–67 yr old, average age 30.1 ± 16.18 yr; 9 women, 8 men) were recruited from a Humboldt University database. This database contains both students and members of the general public. We chose a sample consisting of both students and nonstudents because we did not have a reason to exclude nonstudents or older subjects, wanted a more representative sample, and had a method to recruit them. With the approved recruitment method, this was accomplished by using a wide age range (i.e., subjects were not excluded on basis of age). We included age as a covariate of no interest in relevant analyses. Exclusion criteria included reported diagnosis of any cognitive or psychiatric disorder and/or missing more than three previous scheduled experiments. Handedness was confirmed by an Edinburgh Handedness Inventory score > 40 (Oldfield 1971). Subjects were reimbursed 126 €. Six subjects also participated in an independent behavioral experiment. The study was approved by the Ethical Committee of Humboldt-Universität zu Berlin, the Berlin Center for Advanced Neuroimaging (BCAN, no. 112), and all subjects gave written informed consent.

Stimuli

Twenty-four symbolic (arabic digits) multiplication problems (for problem set see Katz and Knops 2014) were categorized as simple (1 digit × 1 digit, 12 problems) or complex (2 digits × 1 digit, 12 problems). The average problem size (correct choice value) was 30.5 (SD = 12.5) for simple problems and 58.7 (SD = 15.3) for complex problems. The task design was identical to the symbolic multiplication portion of a previously reported behavioral study (Katz and Knops 2014) and similar to previous mental addition and subtraction tasks (Knops et al. 2009b, 2013). To adapt the task for functional imaging and testing complexity, the problems were organized into shorter blocks, simple and complex multiplication problems were separated, and the reaction time (RT) was kept constant. Consistent with previous versions (Katz and Knops 2014), the correct result (C) and six incorrect results were created in a geometric series (C × 1.5^i, i ∈ {−3, −2, −1, 2, 3}). To control for parity, response alternatives were rounded to the same parity as the correct result. The parity of the operands and the correct choice was also balanced between conditions; both conditions had 6 even first operands and 6 odd, 7 even second operands and 5 odd, and 10 even correct choices and 2 odd. Response choices not a multiple of either operand (e.g., “7” for 4 × 3) can present a potential confound. Subjects might easily eliminate these choices, making some trials easier than others. To prevent this confound, easy-to-eliminate response choices were balanced as much as possible. There were 42 of these response choices for simple problems and 50 for complex problems. Two sets of five response choices were used to vary the position of the correct choice relative to alternatives and prevent the strategy of always choosing the middle value. In the low range (first 5 of 7), the correct choice was the 4th of 5 and in the high range (last 5 of 7) the 2nd of 5 (ranked by value). The problem was presented horizontally for 2 s, followed by five response choices presented in a circle for 4 s (Fig. 1, A and B).

Scanning Procedure

During four 8.9-min functional runs (267 volumes/run), problems were presented in twelve 30-s task blocks, with five problems in each block. The simple (Fig. 1A) and complex (Fig. 1B) symbolic multiplication blocks were intermixed with other task blocks beyond the scope of the present article. Before each block, a blank screen was presented for 1 s, followed by instructions for 1 s and a central fixation dot for 10.3 s. The blocks were presented in random order with two blocks of each condition per run. Each problem was repeated four times (once per run), twice for each set of response choices, for a total of 96 symbolic multiplication trials.

Responses were made with a joystick (HH-JOY-4) or a trackball (HHSC-TRK-2) (Current Designs, http://www.curdes.com/) positioned in the subject’s right hand, with a response button under the left index finger. The trackball was used by two subjects because of technical problems with the joystick. Both devices required two hands—one to move the joystick or trackball and one to push the response button. To ensure that subjects were comfortable using the response device, a simple number-matching task was performed during the structural scan acquisition.

Image Acquisition

Scanning was performed on a Siemens 3-T Trio with a 12-channel head coil. Coverage was focused on cerebellar regions of interest (ROIs) (namely, VI), and thus complete coverage was not possible in all subjects. First, an optimized high-resolution 3D T1-MPRAGE structural scan with a 256 × 256 × 192 FOV was acquired (TE = 2.92 ms; TI = 900 ms; TR = 1,900 ms; flip angle = 9°; resolution =...
1 mm isotropic; parallel imaging, GRAPPA = 2). Next, gradient recalled-echo (GRE) images were acquired for spatial distortion correction during preprocessing (TE = 5.19 ms/7.65 ms, TR = 400 ms, flip angle = 60°). Finally, to measure BOLD signal, a T2-weighted axial EPI sequence with a 192 × 192 FOV was acquired (TE = 30 ms, TR = 2,000 ms, flip angle = 78°; resolution, 3 × 3 mm; matrix size, 64 × 64; slice thickness, 3 mm; slice gap, 25%; sequential descending slice order).

Data Analysis

All data analysis was conducted with a standard SPM8 process unless otherwise noted. In particular, because we were interested in the cerebellum, fMRI data analysis was done without thresholding (see fMRI data analysis). An explanation of the process, including all standard settings, is provided for completeness (Poldrack et al. 2008).

Preprocessing. Preprocessing was done with Statistical Parametric Mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) using standard distortion correction and indirect normalization preprocessing steps and settings (distortion correction, realignment, slice-time correction, coregistration, segmentation, normalization, smoothing). The FieldMap toolbox (http://www.fil.ion.ucl.ac.uk/spm/toolbox/fieldmap/) was used to address spatial distortions in EPI images and improve registration accuracy. Reconstructed phase and magnitude images from the GRE sequence were used to create an unwarped field map, which was then converted to a voxel displacement map (Hutton et al. 2002). To correct for motion, images in each run were registered to the first image. The optimum transformation was calculated with second-degree B-spline interpolation. Unwarping was performed on smoothed (4-mm full-width half-maximum (FWHM)) images, with pitch and roll first-order effects, using 12 basis functions for each dimension, leaving out the third dimension (12 × 12 × *; regularization, 1; regularization factor, medium; Taylor expansion point, average). Movement parameters were reestimated after each iteration (maximum iterations, 5). Images were resliced (4th-degree B-spline) with masking of voxels outside the original image and then slice-time corrected to the first functional image (i.e., slice 33). The anatomical image was coregistered to the mean functional image using normalized mutual information, with a separation of 4 mm followed by 2 mm, and the joint histogram was then smoothed with Gaussian smoothing (7-mm FWHM). Next, coregistered anatomical images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) with affine regularization (ICBM European brain template) and very light regularization (bias regularization, 0.0001; warping regularization, 1; warp frequency cutoff, 25; bias FWHM cutoff, 60 mm; sampling distance, 2). Using parameters from segmentation, functional and anatomical images were normalized to the MNI template with trilinear interpolation and resampled to a voxel size of 3 × 3 × 3 mm. Finally, images were smoothed with a kernel twice the voxel size (6-mm FWHM). This was the final smoothing step (SPM “smooth”). The previous smoothing steps are standard in SPM, although usually not reported, and were left unchanged.

fMRI data analysis. The functional data were modeled with a general linear model (GLM) with regressors for each experimental condition and rest, as well as six motion parameters as covariates. In certain situations, the default masking threshold (minimum intensity of included voxels) in SPM can exclude voxels necessary for analysis even if they are included in a user-defined explicit mask, giving Fig. 1. Mental arithmetic task and behavioral validation. Response selections were made with a joystick or trackball (see Scanning Procedure). Five problems were presented in each 30-s block, followed by 12.3 s of rest. A: the simple condition had 1-digit × 1-digit multiplication problems. B: the complex condition had 2-digit × 1-digit multiplication problems. C: mean RT was significantly greater for complex than simple problems. D: mean % correct was significantly greater for simple than complex problems. Results of paired t-tests are shown. Error bars represent 95% confidence interval.
potentially false negative results (Ridgway et al. 2009). The cerebellum is susceptible to this problem, and the default SPM settings will likely result in an analysis mask that excludes most of the cerebellum. Therefore, to ensure inclusion of the cerebellum, first-level and second-level analysis were done without thresholding masking (masking threshold, −inf). A liberal within-brain mask from the O’Connor lab was used for first-level analysis (http://akiraconor.org/2010/03/10/whole-brain-mask/). Second-level analysis was done without implicit masking, with an explicit mask (threshold, t1 > 0.5) created from the gray and white matter image templates to minimize CSF.

Anatomical labeling. We used three atlases in our analysis: 1) the Anatomy Toolbox Probabilistic Histological Atlas (CYTO) (used for seed region masks and cerebral results when possible), 2) the Probabilistic Atlas of the Human Cerebellum (CB) (used for seed region masks and cerebellar results), and 3) Automated Anatomical Labeling (AAL) (used for labeling results only). Equivalencies between these as well as many other atlases can be found with the Online Brain Atlas Reconciliation Tool (OBART) (http://qni.bu.edu/obart) (Bohland et al. 2009). CYTO was used to define all parietal seed regions (IPL: Caspers et al. 2006, 2008; IPS: Choi et al. 2006; Scheperejans et al. 2008a, 2008b) and CB (Diedrichsen et al. 2009, 2011) to define all cerebellar seed regions. Both toolboxes are part of the SPM Anatomy Toolbox (Eickhoff et al. 2005). The atlases were chosen to improve biological plausibility through the use of cytoarchitectonically defined regions. When possible, CYTO was also used to label resulting connected cerebral clusters in PPI analysis, as well as cerebral clusters in local BOLD activity analysis. When cerebral clusters covered multiple CYTO regions (with no clear assignment) or did not correspond to a CYTO region, familiar AAL labels were used.

Seed regions. The cerebellar seed regions were cerebellar lobules VI (hemispheric, HVI; vermal, vVI), VIla/CrusI, and VIla/CrusII. The exploratory cerebellar seed regions were lobules I–IV and V (Fig. 2B). The IPL seed regions were rostral/SMG regions parietal F opercular (PFop), parietal F tenuicorticalis (PFt), parietal F columnar and magnocellular (PFcm), intermediate/SMG regions parietal F (PF) and parietal F magnocellular (PFm), and caudal/AG regions parietal G anterior (PGa) and parietal G posterior (PGp), where F and G are letters originally chosen by von Economo and Koskinas (S. Caspers, personal communication; Caspers et al. 2013; von Economo and Koskinas 1925). The IPS regions were hIP1, hIP2, hIP3 (Fig. 2A).

BOLD activity analysis. To determine task-relevant seed regions, ROI analysis was conducted with small-volume correction (SVC). Within each ROI, t-tests were used to compare complex to simple multiplication (“complex − simple”) and family-wise error (FWE) was used to correct for multiple comparisons (FWE P < 0.05). To visualize whole-brain activation (i.e., complex > simple) and deactivation (i.e., simple > complex) patterns, t-tests were used to compare complex to simple multiplication (“complex − simple”) and significant clusters (cluster-level FDR P < 0.05, to match PPI data, see Planned comparisons) of activation and deactivation were color-coded and overlaid on the ch2bet template (smoothed to match functional data, 6-mm FWHM).

Connectivity analysis. To investigate complexity-related changes in connectivity, a generalized form of PPI analysis (gPPI) was used (McLaren et al. 2012). PPI was chosen because of its accurate reflection of neuronal-level connectivity and decreased susceptibility to hemodynamic and scanning parameters (e.g., TR) (Kim and Horwitz 2008). Additionally, gPPI allows the inclusion of all conditions in a single model, which more accurately reflects the experimental environment (McLaren et al. 2012). First, anatomical seed ROIs were created (see Seed regions). Except for exploratory seed regions, we screened potential regions using significant BOLD activity changes (Supplemental Table S1). For each seed region, the first eigenvariance was extracted from the deconvolved BOLD signal. This neural activity was used to generate the interaction term (neural activity × task condition), which was then reconvolved using the hemodynamic response function (HRF). The final gPPI model included the following regressors: PPI regressors for each condition, task regressors for each condition, a time course for the seed region, and a constant (McLaren et al. 2012).

Planned comparisons. To investigate complexity-related processing, the simple and complex symbolic multiplication conditions were compared (“complex − simple”). Thus positive z values indicate

Fig. 2. Anatomical seed regions. The Anatomy Toolbox was used to create anatomical seed regions. Seed regions are displayed on 5-mm axial slices of the ch2bet template (MRIcon, http://people.cas.sc.edu/orden/mricron/index.html). The z-coordinates (MNI) are shown above slices. A: 10 inferior (IPL) and intraparietal (IPS) seed regions were used. Red shades show IPS regions: hIP1, hIP2, and hIP3. Rostral IPL regions are shown in blue shades: PFcm, PFop, and PF. Intermediate IPL regions are shown in yellow shades: PF and PFm. Caudal IPL regions are shown in violet shades: PGa and PGp. B: 4 cerebellar seed regions were used. Anterior cerebellar seed regions are shown in green shades: lobules I–IV (as single region) and lobule V. Posterior cerebellar seed regions are shown in orange shades: hemispheric lobule VI (HVI), vermal lobule VI (vVI).
greater activity in complex multiplication (complex > simple) and negative z values indicate greater activity in simple multiplication (simple > complex). Correction for multiple comparisons was made at the cluster-level topological FDR \( P < 0.05 \) threshold (SPM8), unless otherwise noted. For connectivity data, small clusters significant only at the peak-level voxelwise FDR \( P < 0.05 \) (xjview, http://www.alivelearn.net/xjview) are also reported, along with complete uncorrected results \( (P < 0.001, k \geq 10) \), in the Supplemental Materials.

RESULTS

Behavioral

Symbolic multiplication data from a previously published behavioral study (Katz and Knops 2014) was reanalyzed using the simple vs. complex distinction. The previous study analyzed all symbolic multiplication problems together and did not compare simple to complex multiplication. To confirm that the complex multiplication condition was more difficult than the simple multiplication condition, accuracy (% correct) and RT were compared. Participants responded 428 ms faster and were 8% more accurate on simple multiplication problems. Significance was confirmed with paired t-tests. There was a significant difference in RT between simple (mean = 1,485.58 ms, SD = 426.45) and complex (mean = 1,914.30 ms, SD = 617.29) multiplication \( t(15) = -4.7, P < 0.001 \). There was also a significant difference in accuracy between simple (mean = 89.71%, SD = 8.49) and complex (mean = 82.29%, SD = 16.19) multiplication \( t(15) = 3.0, P = 0.009 \). This suggests that our distinction between simple and complex problems is consistent with behavioral indicators of complexity.

These findings were replicated with the response data collected during scanning. Only six subjects participated in both the previous behavioral and present fMRI studies. Participants responded 189 ms faster and were 11% more accurate on simple multiplication problems. Again, there was a significant difference in RT between simple (mean = 1,938.64 ms, SD = 339.28) and complex (mean = 2,127.96 ms, SD = 253.17) multiplication \( t(15) = -5.3, P < 0.001 \) [Fig. 1C]. There was also a significant difference in accuracy between simple (mean = 95.46%, SD = 5.60) and complex (mean = 83.61%, SD = 14.96) multiplication \( t(15) = 3.3, P = 0.004 \) [Fig. 1D]. This replication confirms our simple vs. complex distinction. Furthermore, it indicates that subjects were engaged in the task, able to use the response device, and not responding randomly during scanning.

BOLD Activity

Inferior parietal, frontal, and cerebellar regions that are activated by demanding tasks such as complex mental arithmetic (Arsalidou and Taylor 2011; Wu et al. 2009; Zago et al. 2001) should be activated in complex multiplication relative to simple. This was confirmed with whole-brain BOLD GLM analysis (peak FDR \( P < 0.05, k \geq 10 \)). A second-level t-test comparing complex and simple multiplication (“complex − simple”) revealed a pattern of parietal (SPL, IPL, IPS), frontal, thalamic, and posterior cerebellar activations and posteromedial (e.g., retrosplenial, cingulate, AG) deactivations (Fig. 3). This suggests that the experimental manipulation was eliciting brain activity consistent with previous findings (Arsalidou and Taylor 2011; Wu et al. 2009; Zago et al. 2001).

BOLD activity in potential seed regions was analyzed with SVC and FWE correction for multiple comparisons. Although PPI is itself an indicator of task involvement (similar to traditional BOLD contrasts), when ROI analysis (SVC) was performed for each a priori seed region the majority showed task-related BOLD activity changes (Supplemental Table S1). Cerebellar regions HVI, vVI, and VIIa/CrusI had significant task-related BOLD signal changes. All parietal regions except PFt and right PFop had significant task-related BOLD signal changes.

Effective Connectivity

PPI analysis was performed using the selected cerebellar and parietal seed regions (Fig. 2). Second-level t-tests were used to compare complex and simple multiplication (“complex − simple”). Both increased (\( t > 0, \) complex > simple) and decreased (\( t < 0, \) simple > complex) connectivity were considered. Although accuracy and RT are behavioral proxies for complexity, they may also be confounds. Therefore, significant connectivity changes were tested using age to control for the wide age range, accuracy to control for error-related processing (simple % correct − complex % correct), and RT to control for time on task (complex RT − simple RT). Age, accuracy, and RT were entered as covariates of no interest.

Cerebellar connectivity. To test complexity-related connectivity changes of cerebellar seed regions, PPI analysis was performed with the following seed regions: HVI and vermal VI, as well as I–IV and V (these were not significant but included for exploratory analysis of finger tapping regions) (Fig. 2B). We found significant complexity-related connectivity changes for both the hemispheric and vermal portions of posterior lobule VI but not for anterior lobules I–IV or V. For all significant seed regions, connectivity significantly decreased in complex multiplication compared with simple multiplication (i.e., simple > complex) (Table 1).

PPI analysis is susceptible to false negatives, and this could be the cause of the exclusively decreased connectivity. A relaxed statistical threshold might reveal a mix of increased and decreased, or even mostly increased, connectivity. Therefore, we performed the same analysis without correction for multiple comparisons (uncorrected \( P < 0.001, k \geq 10 \)). Interestingly, this pattern of decreased cerebro-cerebellar connectivity persisted when the more liberal uncorrected threshold was used (Supplemental Table S2).

Both the left and right hemispheres of HVI decreased connectivity to partially overlapping left parietal areas, while left HVI decreased connectivity to additional left frontal and cingulate areas (Table 1; Fig. 4A). Left lobule HVI had significant complexity-related decreases (i.e., when complexity increased, connectivity decreased) in connectivity to three predominantly left hemisphere clusters: a left IPL cluster (\( k = 281 \)), a left SMA cluster (\( k = 46 \)), and a left middle frontal cluster (\( k = 45 \)). Right lobule HVI had significant complexity-related decreases in connectivity to one left IPL cluster (\( k = 187 \)). The majority of clusters remained significant (cluster FDR \( P < 0.05 \) after controlling for age, RT, and accuracy. In some cases, controlling for confounds improved the model. Previously nonsignificant PPI clusters (Supplemental Table S2)
reached the cluster FDR $P < 0.05$ threshold: L HVI decreased connectivity to a right IPL cluster (after controlling for age: MNI peak, 54 28 46; $z = 4.06$, cluster FDR $P = 0.036$, $k = 35$; after controlling for RT: MNI peak, 54 28 46; $z = -3.94$, cluster FDR $P = 0.035$, $k = 35$). R HVI decreased connectivity to a left SMA cluster (previously nonsignificant, Supplemental Table S2) (after controlling for RT: MNI peak, 3 16 49; $z = 4.33$, cluster FDR $P = 0.030$, $k = 44$).

Both the left and right sides of vVI decreased connectivity to partially overlapping bilateral parietal areas (Table 1; Fig. 4B). Left vermal lobule VI had significant complexity-related decreases in connectivity to two clusters: a left IPL cluster ($k = 96$) and a right IPL cluster ($k = 44$). Right vermal lobule VI had significant complexity-related decreases in connectivity to two clusters: a left IPL cluster ($k = 235$) and a right IPL cluster ($k = 65$). These clusters remained significant after controlling for age (covariate of no interest). However, a previously significant L vVI R postcentral/supramarginal cluster was no longer significant after controlling for accuracy (peak MNI, 54 34 49; $z = -3.82$, cluster FDR $P = 0.063$, $k = 37$), and cluster size decreased but remained significant after controlling for RT (peak MNI, 54 31 43; $z = 3.83$, cluster FDR $P = 0.047$, $k = 39$).

For anterior cerebellar seed regions, although no significant complexity-related connectivity changes were found with the cluster-level FDR correction, left and right lobules I–IV had significant connectivity changes with the peak-level FDR correction. Left I–IV decreased connectivity to a small left superior frontal cluster ($k = 19$), and right I–IV decreased connectivity to a small left middle cingulate cluster ($k = 13$) (peak FDR $P < 0.05$) (Supplemental Table S2). Lobule V did not have any significant connectivity changes with either the peak- or cluster-level FDR correction for multiple comparisons.

In summary, connectivity changes between cerebellar lobule VI and overlapping parietal areas contribute to complexity-related processing. Furthermore, these connectivity changes are mostly independent of age, error processing, or RT. Both the left and right hemispheric VI (HVI) lobules connected to predominantly left hemisphere areas. After controlling for age, a right IPL cluster became significant. Vermal VI lobules connected to bilateral parietal areas. In complex multiplication, we found relative decreases in connectivity. For all cerebellar seed regions, connectivity decreased in complex compared with simple multiplication. In other words, connectivity was greater in simple multiplication than in complex multiplication.

**Parietal connectivity.** To determine complexity-related changes in connectivity for parietal seed regions, we performed PPI analysis with the following seed regions: PFop (left only), PFcm, PF, PFm, PGa, PGp, hIP2, hIP2, and hIP3 (Fig. 2A). We found significant complexity-related connectivity changes for rostral and intermediate portions of the IPL but not for caudal...
Table 1. Cerebellar connections (complex - simple)

<table>
<thead>
<tr>
<th>Seed</th>
<th>Connections</th>
<th>Peak x</th>
<th>y</th>
<th>z</th>
<th>k</th>
<th>z</th>
</tr>
</thead>
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<tr>
<td>L HVI</td>
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</tr>
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<td>46</td>
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<td></td>
</tr>
<tr>
<td>L Postcentral</td>
<td>-39</td>
<td>-22</td>
<td>43</td>
<td>-4.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L SMA</td>
<td>-3</td>
<td>-4</td>
<td>55</td>
<td>46</td>
<td>-4.26</td>
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</tr>
<tr>
<td>R Mid Cing.</td>
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</tr>
<tr>
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<td>L vVI</td>
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<tr>
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<td>31</td>
<td>-3.93</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>-3.87</td>
<td></td>
</tr>
<tr>
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<td>43</td>
<td>-3.37</td>
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</tr>
<tr>
<td>R vVI</td>
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</tr>
<tr>
<td>L IPL</td>
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<td>46</td>
<td>-4.36</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>-28</td>
<td>43</td>
<td>-3.87</td>
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</tr>
<tr>
<td>R IPL</td>
<td>39</td>
<td>-40</td>
<td>46</td>
<td>-3.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Connections are listed by AAL labels based on the MNI atlas because not all clusters could be classified with Anatomy Toolbox. Supplemental Table S3 contains Anatomy Toolbox classifications, where available. H, hemispheric; v, vermal. Cluster-level FDR \( P < 0.05 \).

portions or the IPS. In contrast to cerebellar seed regions, parietal seed regions increased connectivity in complex multiplication compared with simple multiplication (i.e., complex > simple). As with cerebellar findings, we relaxed the statistical threshold to see whether the exclusively increased parietal connectivity might be due to false negatives. The pattern of increased parietal connectivity persisted when the more liberal uncorrected threshold was used (\( P < 0.001 \), \( k \geq 10 \)), with two exceptions: left PFcm to right hippocampus and right PGp to left SMA. However, these uncorrected data should be interpreted with caution (Supplemental Table S3).

For rostral IPL areas both the left and right hemispheres of PFcm increased connectivity to partially overlapping portions of the right precuneus (L: \( k = 37 \); R: \( k = 47 \)), while right PFcm increased connectivity to an additional right medial orbital frontal area (\( k = 54 \)) (Table 2; Fig. 5A). The clusters remained significant after correcting for age, accuracy, and RT (cluster FDR \( P < 0.05 \)), except for the left PFcm R precuneus cluster after RT (peak MNI, \( 6 - 58 \ 22; z = 3.99; \) cluster FDR \( P = 0.063 \), \( k = 37 \)). After controlling for age, a previously nonsignificant left PFcm right medial orbital frontal cluster (Supplemental Table S3) reached the cluster FDR \( P < 0.05 \) threshold (peak MNI, \( 3 53 -2; z = 3.63; \) cluster FDR \( P = 0.022 \), \( k = 30 \)). Left PFop also increased connectivity to a right medial orbital frontal area (\( k = 51 \)) (Fig. 5B). This cluster remained significant after controlling for age and RT (cluster FDR \( P < 0.05 \)) but was not significant after controlling for accuracy (peak MNI, \( 9 59 -8; z = 4.11; \) cluster FDR \( P = 0.099 \), \( k = 36 \)).

For intermediate IPL areas only left PFm had significant complexity-related connectivity changes, while right PFm and PF had no significant connectivity changes, even at the uncorrected \( P < 0.001 \) (\( k \geq 10 \)) threshold (Supplemental Table S3). Left PFm increased connectivity in complex multiplication to a right SPL area, including a right AG peak (\( k = 96 \)) (Fig. 6). This cluster remained significant after controlling for age, accuracy, and RT (cluster FDR \( P < 0.05 \)). Neither right PFm, PF, any caudal IPL areas (PGa, PGp), nor any IPS areas (hIP1, hIP2, hIP3) had significant complexity-related changes in connectivity after correction for multiple comparisons. For IPS areas, even at the uncorrected \( P < 0.001 \) (\( k \geq 10 \)) threshold, only hIP1 and right hIP2 had any significant connectivity changes (Supplemental Table S3).

These results suggest that connectivity changes from rostral parietal areas to precuneus and frontal areas, as well as changes from a left intermediate parietal area to a right SPL area, underlie complexity-related processing. Although some of these connectivity changes may be confounded by RT (L PFcm seed to R precuneus) and accuracy (L PFop seed to R medial orbital frontal), the majority remained significant or became
significant after controlling for such confounds. In complex multiplication, we found relative increases in connectivity. For all parietal seed regions, connectivity increased in complex compared with simple multiplication. In other words, connectivity was greater in complex multiplication than in simple multiplication. This suggests that increased parietal-parietal and parietal-frontal connectivity supports complex tasks.

Taken together, our results reveal that increased complexity is associated with decreased cerebellar-parietal and cerebellar-frontal connectivity but increased parietal-parietal and parietal-frontal connectivity (Fig. 7).

**PPI-BOLD Overlap**

To visualize the spatial overlap between whole-brain BOLD signal changes and PPI connectivity changes, significant PPI and BOLD contrasts were overlaid on the smoothed template image (Fig. 8). It should be noted that points of spatial overlap do not represent statistically determined common activity but are simply a way to visualize BOLD and PPI results simultaneously. PPI clusters only overlapped with BOLD complex clusters. There was no significant overlap with BOLD simple > complex clusters (not shown in Fig. 8). For cerebellar seed regions, there were overlapping areas of decreased cerebellar-parietal connectivity (VI seeds to L-IPL) but increased BOLD activity. For parietal seed regions, there were overlapping areas of increased interhemispheric parietal connectivity (L-PFcm seed to R-SPL) and BOLD activity in the right SPL (Table 3). Cerebellar connectivity changes were anterior to activity changes, whereas parietal were posterior. The overlapping areas in PPI and BOLD images do not necessarily repre-
sent the same neuronal populations and should be interpreted with caution. PPI analysis also revealed additional brain regions involved in complexity-related processing but not seen in BOLD contrasts. Areas visible only in PPI contrasts demonstrate those involved in complexity-related processing but invisible in traditional BOLD contrasts. This may be due to a balance of inhibitory and excitatory input canceling out BOLD signal changes.

**DISCUSSION**

In the present study, we tested cerebellar and parietal connectivity changes as a function of complexity. Our primary hypothesis was that cerebellar lobule VI, given its role in complex vs. simple tasks, as well as attention (i.e., salience) networks would have significant complexity-related connectivity changes. Our results generally supported this hypothesis: lobule VI had significant complexity-related connectivity changes. We also anticipated increased connectivity in complex multiplication. Surprisingly, we found that cerebellar-parietal, cerebellar-cingulate, and cerebellar-frontal connectivity decreased with increasing complexity, whereas parietal-parietal and parietal-frontal connectivity increased. Although these parietal findings are consistent with previous research, fewer regions had significant connectivity changes than we expected. In cerebellar seed regions, there were also differences between hemispheric and vermal connectivity patterns. In complex multiplication, all four portions of lobule VI (L-HVI, R-HVI, L-vVI, R-vVI) decreased connectivity to partially overlapping left IPL areas. Additionally, both

Table 3. **Overlap of BOLD and PPI contrasts**

<table>
<thead>
<tr>
<th>Region</th>
<th>Peak</th>
<th>PPI Seed</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>k</th>
<th>PPI Seed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar PPI mask (simple &gt; complex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L IPL</td>
<td>−51</td>
<td>−40</td>
<td>49</td>
<td>66</td>
<td>5.37</td>
<td>L and R HVI</td>
<td></td>
</tr>
<tr>
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<td>−33</td>
<td>−49</td>
<td>43</td>
<td>4.77</td>
<td>L HVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L IPL</td>
<td>−39</td>
<td>−46</td>
<td>49</td>
<td>4.72</td>
<td>L and R HVI R vVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal PPI mask (complex &gt; simple)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R SPL</td>
<td>33</td>
<td>−64</td>
<td>49</td>
<td>30</td>
<td>5.04</td>
<td>L PFm</td>
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</tr>
<tr>
<td>R Sup. Occ.</td>
<td>27</td>
<td>−70</td>
<td>46</td>
<td>4.09</td>
<td>L PFm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPI clusters overlapped with BOLD complex > simple clusters only; there was no significant overlap with BOLD simple > complex clusters. All significant at cluster-level FDR P < 0.05.

Fig. 7. Connectivity network underlying complex vs. simple multiplication. A network diagram summarizing significant (cluster FDR P < 0.05) PPI results was visualized with BrainNet Viewer (Xia et al. 2013; http://www.nitrc.org/projects/bnv/). Overlapping clusters are shown as single sphere for clarity. PPI cluster sphere size is proportional to cluster size. Seed region spheres are single size for clarity.

Fig. 8. Overlap between PPI and BOLD. For the contrast “complex − simple,” cerebellar connectivity decreases [i.e., simple > complex (S > C)], parietal connectivity increases [i.e., simple > complex (S > C)], and BOLD activity increases (C > S) were overlaid on 5-mm slices of the ch2bet template (smoothed to match functional data, 6-mm FWHM). In the L IPL, there were overlapping areas of decreased cerebellar-parietal connectivity but increased parietal activity (k = 66, purple). In the R SPL, there were overlapping areas of increased IPL-SPL connectivity (L-PFm to R-SPL, k = 30, yellow) and R-SPL activity.

**Fig. 7.** Connectivity network underlying complex vs. simple multiplication. A network diagram summarizing significant (cluster FDR P < 0.05) PPI results was visualized with BrainNet Viewer (Xia et al. 2013; http://www.nitrc.org/projects/bnv/). Overlapping clusters are shown as single sphere for clarity. PPI cluster sphere size is proportional to cluster size. Seed region spheres are single size for clarity.

**Fig. 8.** Overlap between PPI and BOLD. For the contrast “complex − simple,” cerebellar connectivity decreases [i.e., simple > complex (S > C)], parietal connectivity increases [i.e., simple > complex (S > C)], and BOLD activity increases (C > S) were overlaid on 5-mm slices of the ch2bet template (smoothed to match functional data, 6-mm FWHM). In the L IPL, there were overlapping areas of decreased cerebellar-parietal connectivity but increased parietal activity (k = 66, purple). In the R SPL, there were overlapping areas of increased IPL-SPL connectivity (L-PFm to R-SPL, k = 30, yellow) and R-SPL activity.
sides of vVI decreased connectivity to overlapping right parietal areas.

Connectivity Changes in Parietal Seed Regions

The finding of increased parietal-parietal and parietal-frontal connectivity during complex tasks is consistent with previous numerical task-related connectivity research. Using PPI, non-symbolic (dot arrays) addition and subtraction vs. simple shape matching was associated with increased interhemispheric parietal and parietal-frontal connectivity (Park et al. 2013). Similarly, we found that during complex mental calculation rostral IPL regions increased connectivity to frontal and prefrontal areas and intermediate IPL regions increased connectivity to SPL and AG areas. Using Granger causality, Krueger et al. (2011) found that increasing difficult symbolic multiplication was associated with increased fronto-parietal and parietal-parietal connectivity. These expected parietal connectivity changes suggest that the cerebellar connectivity changes are not due to idiosyncrasies in our experiment.

Connectivity Changes in Cerebellar Seed Regions

Understanding the cerebellum’s role in nonmotor behavior and cognition has been limited by the lack of task-driven seed-based (e.g., PPI) connectivity research (Keren-Happuch et al. 2014). Cerebellar, parietal, and frontal BOLD coactivation in cognitive tasks has been interpreted as task-related connectivity between lobules VI–VIIa/CrusI, prefrontal, and parietal regions (Stoodley et al. 2012). Consistent with this interpretation, we found significant complexity-related connectivity changes between some of these regions, demonstrating task-related cerebellar-parietal and cerebellar-frontal connectivity.

Resting-state research also shows cerebellar-parietal and cerebellar-frontal connectivity (Buckner et al. 2011; Habas et al. 2009; Krienen and Buckner 2009; O’Reilly et al. 2010). Similar to Buckner et al. (2011), we found significant connectivity changes between HVI and parts of the Salience network (N8 in 17-network estimate), the Ventral attention network (N7 in 17-network estimate), and the Control A network (N12 in 17-network estimate). Unlike Buckner et al. (2011), we found connectivity between VI rather than VIIb–VIIa and CrusI and regions included in Dorsal attention B (N6 in 17-network estimate) (Baker et al. 2014; Yeo et al. 2011). However, because of the potential for false negatives in PPI as well as the difficulty in translating correlational functional connectivity methods to task-based effective connectivity methods, the exact reasons for this remain unknown. One possibility is that, rather than being a sensitivity issue, task complexity targets a specific subset of this network. Although this cannot be determined from nonsignificant results, it is an interesting question for future research. Our findings expand on functional connectivity findings and describe some of the dynamic, task-driven changes in these intrinsic connectivity networks.

Despite the relative nature of BOLD and PPI contrasts, the fMRI literature frequently focuses on increased activity and connectivity. A brain region’s failure to activate (i.e., hypactivity) or connect (i.e., hypoconnectivity) can certainly impair behavior and cognition (Hester et al. 2009; Kaufman et al. 2003; McCarthy et al. 2013; Pizzagalli et al. 2001). However, deactivation in one task relative to another or in a given task over time can also be associated with successful learning. In healthy control subjects, CrusI deactivation was associated with practice and successful automation (Balsters and Ramnani 2011). Consistent with this, we found that CrusI activity decreased for simple multiplication, a process that is likely practiced and automated in educated adults (e.g., LeFevre et al. 1996; Smith-Chant and LeFevre 2003). Although we do not know if this deactivation was necessary for task performance, clinical research shows that failure to deactivate (i.e., hyperactivity) or decrease connectivity (i.e., hyperconnectivity) can be detrimental. Frontal and cerebellar BOLD hyperactivity has been shown to occur alongside frontal-parietal hypoconnectivity following repeated concussions, suggesting an inhibitory failure (Hampshire et al. 2013). Parietal hyperactivity was associated with age-related memory impairment (Miller et al. 2008). This hyperactivity suggests a failure to inhibit, due to either an overactive excitatory loop or an impaired inhibitory loop. Whether a cerebellar-parietal or cerebellar-frontal loop, similar to the one we have identified, could contribute to parietal or frontal deactivation failure is a question for future research. However, there is evidence for pathological connectivity between the cerebellum and the parietal lobe. Impaired response inhibition in chronic cannabis users was related to parietal-cerebellar hyperconnectivity (Behan et al. 2014). Future research should consider the role of both cerebellar hyperconnectivity and hypoconnectivity.

Our finding of decreasing connectivity with increasing complexity is particularly interesting given the body of research showing cerebellar activation in complex tasks. Two recent meta-analyses of brain imaging data (BOLD fMRI and PET) show that lobules VI and VII are involved in a variety of cognitive tasks (Keren-Happuch et al. 2014; Stoodley and Schmahmann 2009). Consistent with this, we found that lobules VI and VIIa/CrusI, but not lobules I–IV or V, are involved in relatively complex tasks. Specifically, lobules VI and VIIa/CrusI had increased BOLD activity in complex multiplication. Lobule VI was also involved in a complexity-related connectivity network, but, surprisingly, it decreased connectivity as complexity increased. This novel finding of decreased connectivity advances understanding of cerebellar-cerebral connectivity changes underlying cognition, suggesting that cerebellar and parietal coactivation is not always associated with increased connectivity. Rather, these regions may participate in separate networks in more complex tasks and connect during simple tasks. Future research will need to test this hypothesis across a variety of domains.

Decreasing cerebellar-cerebral connectivity with increasing task complexity could be part of the cerebellum’s role in appropriate implementation of cognitive and behavioral processes (Schmahmann 1991, 1998; Schmahmann and Caplan 2006). Of the three nonexclusive explanations for the cerebellum’s role in cerebellar-cerebral circuits (Strick et al. 2009), our findings are consistent with both the speech component of sensorimotor imagery (Ackermann et al. 1998; Hanakawa et al. 2008; Lotze et al. 1999) and adaptive plasticity underlying learning (Gao et al. 2012; Ito 2008; Mauk et al. 1997; Wolpaw and Chen 2006). Subjects may have relied more heavily on inner speech during simple multiplication, and increased connectivity may reflect cerebellar influence on this component. Additionally, simple multiplication is likely a more learned, automated process, and increased connectivity may reflect...
cerebellar influence on this component. Although the third explanation, timing and sequencing (Spencer and Ivry 2013), could still play a role, our results remained significant after controlling for RT. Although certainly related to all three explanations, task difficulty may be a fourth, also nonexclusive, explanation for the cerebellum’s role in cerebellar-cerebral circuits. This fourth role is consistent with dysmetria of thought associated with cerebellar pathologies (Schmahmann 1998).

Our results may be relevant in defining the neural architecture supporting calculation (Klein et al. 2013, 2016). In the number domain, the cerebellum’s role in cerebral number circuits is not well understood. A meta-analysis of brain imaging data found HVI and CrusI activation associated with calculation tasks and HVI activation with noncalculation number tasks (Arsalidou and Taylor 2011). The studies included in this meta-analysis used diverse tasks and baselines, but the majority of the baseline tasks could be considered less complex than the task condition (see Table 1). Our findings of HVI and CrusI activity are consistent with this meta-analysis. Arsalidou and Taylor (2011) hypothesized that the cerebellum may be involved in coordinating visual motor sequencing to respond to task demands under time pressure. Interestingly, our connectivity results remained significant even after controlling for RT. This connectivity change independent of RT suggests that perhaps the task difficulty, independent of visual motor responses under time pressure, may account for the cerebellum’s role in mental calculation. The original triple-code model of numerical cognition hypothesizes that single-digit arithmetic facts bypass general magnitude processing in the parietal lobe and are directly retrieved (Dehaene and Cohen 1995, 1997). However, recent findings have suggested that arithmetic fact retrieval is grounded in magnitude processing. We speculate that the cerebellum might support direct memory retrieval of arithmetic facts by inhibiting (although not necessarily bypassing) parietal magnitude processing activity. Adding to amendments to the triple-code model that have been put forward recently (Klein et al. 2016), we suggest incorporating the differential cerebellar-cerebral connectivity with varying task (e.g., arithmetic) complexity in future neurocognitive models of mental arithmetic.

Overlap Between BOLD Activity and PPI Connectivity

Although the relationship between connectivity and activation measures is not fully understood, examining the overlap between BOLD and PPI changes could lead to new hypotheses. To this end, we looked at the overlap between PPI and BOLD changes and made two observations. First, not all regions identified in PPI analysis were significant in traditional BOLD analysis. This suggests that additional parietal areas may be involved in automated and complex processes but invisible in BOLD activity contrasts because of excitatory/inhibitory input balance (Arthurs and Boniface 2002). The parietal regions identified in PPI connectivity contrasts were generally anterior to those in BOLD activity contrasts. Second, where overlap occurred (e.g., L IPL), there was decreased connectivity in complex multiplication but increased BOLD activity. Consistent with overlapping areas of BOLD deactivation but increased connectivity, GABAergic signaling generally decreases BOLD signal (Chen et al. 2005; Northoff et al. 2007). Future research should test the role of inhibitory cerebellar-parietal loops in automated processes (e.g., multiplication fact retrieval) and the mechanisms by which these regions decrease connectivity with increasing task demands.

Given the classic role of long-term potentiation (LTP) and long-term depression (LTD) in learning and memory, our findings of increased connectivity for simple multiplication may not be so unexpected. LTD has been shown to underlie cerebellar deactivation in learned motor sequences (Ito 2008). Previous fMRI research suggested that CrusI deactivation for more automated tasks may be related to LTD plasticity processes (Balsters and Ramnani 2011). Similarly, an inhibitory GABA loop in simple multiplication is consistent with the cellular mechanisms of learning and memory. Long-range GABAergic neurons involved in synchronous network activity are thought to temporally coordinate neuronal activity in distant brain regions (Caputi et al. 2013). For example, GABAergic neurons have been shown to underlie bidirectional entorhinal-hippocampal inhibitory connectivity (Melzer et al. 2012). MAO-induced (5-HT, norepinephrine) LTP of GABAergic neurons (e.g., Mitoma and Konishi 1999) may be one mechanism driving inhibitory GABA loops in automated processes like arithmetic fact retrieval. Future research with an appropriate animal model could combine retro- and anterograde tracers with in vivo electrophysiological recordings, to examine whether long-range GABAergic neurons underlie the inhibitory loop suggested by our findings.

Limitations

Some limitations should be considered when interpreting our findings. First, seed-based connectivity analysis is sensitive to seed-region selection. We chose to use atlas-defined anatomical regions, but there are many other methods (e.g., functional clusters, spheres around functional peaks, ICA-defined nodes) and each has benefits and limitations. As previously discussed, atlas-based methods may be less sensitive (Patel et al. 2014), yet we still found significant connectivity changes. Second, we chose to use the same number of trials and the same timing in simple and complex blocks. Consequently, subjects might have had slightly more downtime in simple blocks. Greater downtime could be interpreted as more time spent in the default-mode state. While an event-related design would be less affected by downtime, PPI analysis works best with a block design. Self-paced timing is one alternative, although this could introduce intersubject and intercondition variability in the number of calculations per block. Despite this, all results remained after controlling for individual differences in time on task. Third, we used subjects drawn from the general population rather than just students. We feel this addresses concerns over applicability of research results, but it does introduce a wide age range. However, including age as a covariate of no interest did not significantly change results. Fourth, PPI analysis of fMRI data cannot reliably compare task vs. rest; thus it is difficult to know how connectivity changed compared with rest. To our knowledge, basic connectivity in each PPI condition cannot be reliably measured at present. Consequently, we cannot determine the change in connectivity relative to rest for each condition. However, since our conclusions only deal with the change in connectivity between simple and complex cal-
culation, this question, while interesting, is beyond the scope of the present study.

Conclusions

In summary, we found that cerebellar-cerebral connectivity decreased in complex multiplication relative to simple multiplication, whereas interparietal and parietal-frontal connectivity increased. Previous research had demonstrated significant involvement of cerebellar lobule VI in complex cognitive tasks, but its role in cerebellar-cerebral networks was unknown. We found decreased cerebellar-parietal (all VI seeds) and cerebellar-frontal/cerebellar-cingulate (only L-HVI seed) connectivity in complex tasks. This suggests that decreased cerebellar connectivity during complex tasks relative to simple may be important for cognitive and behavioral responses to task demands. Future research might consider whether decreased connectivity for complex tasks occurs through excitatory decoupling.

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AUTHOR CONTRIBUTIONS

C.K. and A.K. conception and design of research; C.K. performed experiments; C.K. analyzed data; C.K. interpreted results of experiments; C.K. prepared figures; C.K. drafted manuscript; C.K. and A.K. edited and revised manuscript. C.K. and A.K. approved final version of manuscript.

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