Ramping dissociates motor and cognitive sequences in the parietal and prefrontal cortices

Abbreviated title: Ramping dissociates motor and cognitive sequences

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Abstract

Humans complete different types of sequences as a part of everyday life. These sequences can be divided into two important categories: those that are abstract, in which the steps unfold according to a rule at super-second to minute time scale, and those that are motor, defined solely by individual movements and their order which unfold at the sub-second to second timescale. For example, the sequence of making spaghetti consists of abstract tasks (preparing the sauce and cooking the noodles) and nested motor actions (stir pasta water). Previous work shows neural activity increases (ramps) in the rostrolateral prefrontal (RLPFC) during abstract sequence execution (Desrochers et al., 2015, 2019). During motor sequence production, activity occurs in regions of the prefrontal cortex (Yewbrey et al., 2023). However, it remains unknown if ramping is a signature of motor sequence production as well or solely an attribute of abstract sequence monitoring and execution. We tested the hypothesis that significant ramping activity occurs during motor sequence production in the RLPFC. Contrary to our hypothesis, we did not observe significant ramping activity in the RLPFC during motor sequence production, but we found significant activity in bilateral inferior parietal cortex, in regions distinct from those observed during an abstract sequence task. Our results suggest different prefrontal-parietal mechanisms may underlie abstract vs. motor sequence execution.

Introduction

Reaching goals in everyday life requires completing sequences of tasks. For example, baking a cake requires following instructions provided by a recipe. The steps of a recipe can be broken down into different sequence types. The abstract sequence details ordered tasks without specific motor actions, such as combining the dry ingredients and preparing the pan. Each of these tasks is comprised of motor sequences of actions, like scooping out the flour and brushing the pan with butter. Thus, sequences can be considered to contain both abstract and motor components. Abstract sequences are defined by a rule that governs the order but not motor identity of steps (Desrochers et al., 2022), while motor sequences, which can be nested into the abstract sequence, are defined by a specific series of actions in a certain order (Hikosaka et al., 2002; Rosenbaum et al., 2007; Yewbrey et al., 2023). Neurally, the rostrolateral prefrontal cortex (RLPFC, also referred to as lateral anterior prefrontal cortex, aPFC) has been shown to be necessary for abstract sequences (Desrochers et al., 2015), but the role of this region in motor sequences remains unclear. Because motor and abstract sequence execution are often together, a common sequence tracking process in the RLPFC may underlie them. The present study tested this possibility by examining neural dynamics in the PFC during motor sequence production.

Motor sequences such as stirring (**Figure 1A**), are supported primarily by activity in motor, premotor and parietal cortices. The premotor cortex, supplementary motor area, and parietal cortex contain information about chunks and position rank in motor sequences (Tanji and Shima, 1994; Yokoi and Diedrichsen, 2019; Russo et al., 2020). The motor cortex is associated with the execution of single movements in sequences (Yokoi et al., 2018; Zimnik and Churchland, 2021; Ariani et al., 2022) and is active during sequences of ordered finger presses (Yewbrey et al., 2023). Thus far, literature shows motor and related cortical regions support motor sequence execution, and the potential contribution of the lateral aPFC in this process remains unclear.

Abstract sequences, however, are supported by prefrontal neural dynamics that may generalize as a tracking mechanism across sequence types. Abstract sequences are not defined by the content of their motor actions; rather, their execution relies on following a structure or rule, such as following a recipe to bake a cake (**Figure 1A**). Previous work showed abstract sequences were supported by ramping, the increase of neural activity, in the rostrolateral PFC (RLPFC) and other regions of the fronto-parietal network (FPN) (Desrochers et al., 2015). Further, this study showed the necessity of this region for sequence completion using transcranial magnetic stimulation. The RLPFC is therefore crucial for the completion of abstract sequences. However, it remained unknown if ramping in this region supports motor sequence completion, as well, which could demonstrate that these dynamics act as a common supporting mechanism for both sequence types.

We tested the hypothesis that RLPFC ramping supports motor sequence production by analyzing data from a previously published study investigating sequences of pre-learned finger presses (**Figure 1B**) (Yewbrey et al., 2023). Contrary to our hypothesis, we did not observe significant ramping activation in RLPFC during motor sequence production. However, we did observe significant ramping activation in parietal and cortical regions such as the ventromedial PFC and inferior parietal cortex, that were distinct from those previously observed during abstract sequences (Desrochers et al., 2015). Further, we determined ramping was increased in the default mode network (DMN) and decreased in the frontoparietal network (FPN) and anterior hippocampus (HPC) during motor sequence production. Our findings point to dissociable fronto-

parietal networks underlying motor and abstract sequence production, suggesting differential circuits define these two sequence types.

Methods

In total, 24 participants completed the original experiment and thus were used as subjects in the present study. Details of study participants, apparatus, and data acquisition can be found in the original study and will briefly be described here (Yewbrey et al., 2023).

Task Design and Procedure

Participants in the original study were trained to produce four 5-finger sequences from memory in a delayed sequence production paradigm (Yewbrey et al., (2023); summarized in Figure 1B). Sequences had defined inter-press intervals (IPIs) and two different orders and timings, making four possible conditions. The timing structures were the same across participants (T1: 1200 ms-810 ms-350 ms-650 ms; T2: 350 ms-1200 ms-650 ms-810 ms). The experiment consisted of "Go" and "No-Go" trials. Go trials began with a sequence cue (a specific fractal image), which was associated with one of the four sequences. The cue was then followed by a screen with a fixation cross of jittered timing, which was followed by a green screen with the image of a black hand. This image cued the onset of sequence production. After the production window, another fixation screen of jittered timing appeared, followed by feedback. No-Go trials followed the same structure as Go trials but lacked the "go" cue (green screen with a black hand). Participants therefore had to remember four total fractal cues that each represented a different sequence (T1O1, T2O1, T1O2, T2O2). During the production period in No-Go trials, the fixation screen was shown for an additional 1000 ms. In the present study, we analyzed only the Go trials. A full description of the task design and procedure can be found in the original neuroimaging study (Yewbrey et al., 2023).

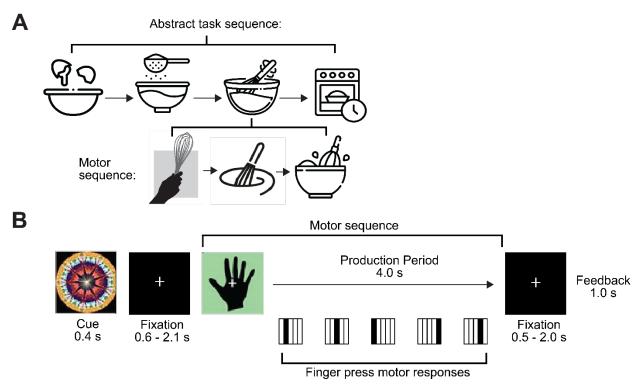


Figure 1. Abstract and motor sequence schematic and behavioral task. A. Abstract sequences contain tasks that do not rely on specific motor actions to complete (e.g., tasks of adding eggs, sifting flour, combining ingredients, and putting them in the oven when baking a recipe). Motor sequences contain tasks that require specific actions to achieve the goal (e.g., to whisk together all the ingredients one might grab the whisk, make a stirring motion, and tap the whisk against the bowl) B. The motor sequence paradigm (adapted from (2023), see Methods for details), from which data was analyzed for the current study. Participants were presented with a cue that signaled the preparation and production of a pre-learned sequence of 5 finger presses. An image of a black hand signaled the "Go" cue, the period in which participants could produce these sequences. Importantly, these sequences are only correct if the specific motor actions (finger presses) are conducted in a particular order and timing (like morse code or playing a piano melody), which separates these sequences in nature from abstract sequences.

Data Acquisition

A Philips Ingenia Elition X 3T MRI scanner using a 32-channel head coil was used for whole-brain imaging. T2*-weighted functional data were acquired across six runs (repetition time, TR = 2.0 s; echo time, TE = 35 ms; flip angle 90°; 60 odd-even interleaved slices; 2.0 mm isotropic voxel size). T1-MPRAGE anatomical scans were acquired at a $0.937 \times 0.937 \times 1$ resolution, with an FOV of $240 \times 240 \times 175$ (A-P, R-L, F-H), encoded in the anterior-posterior dimension. See Yewbrey et al., (2023) for a full description of data acquisition.

Data Analysis

Preprocessing

In the original study, images underwent slice time correction, realignment and unwarping, and EPI images were co-registered to each subject's T1 anatomical scan (see

Yewbrey et al., (2023) for more information). These images were further preprocessed using Statistical Parametric Mapping (SPM12) in Matlab 2023a. Specifically, images were normalized to the Montreal Neurological Institute (MNI) stereotaxic template with affine regularization. smoothed using an 8mm full-width at half-maximum Gaussian kernel, and resampled using trilinear interpolation.

FMRI Models

All general linear models were constructed using Statistical Parametric Mapping (SPM12) software with custom scripts in Matlab 2023a. Onsets and parametric regressors were convolved with the canonical hemodynamic response function (HRF). Onset regressors were additionally convolved with the first time derivative of the HRF. Errors made during sequence production were categorized as separate events and included as onset regressors with a duration of 0 s in the models. To account for variance due to translational and rotational motion (x, y, z, roll, pitch, yaw), we included nuisance regressors.

A subject-specific fixed-effects parametric ramp model was used to estimate beta values related to regressors. This model tests for ramping activity associated with each sequence position (1-5). We constructed regressors for each sequence condition (O1T1, O2T1, O1T2, O2T2), which included a zero-duration onset for each button press during production and a parametric (numbers 1-5) for a linear increase across the five sequence positions. Onset and parametric regressors were estimated hierarchically in SPM, so that variance attributed to parametric regressors was more than that accounted for by stimulus onset alone. The parametric ramp model was based on previously constructed models (Desrochers et al., 2015, 2019) used to assess ramping activity related to sequences. Whole brain contrasts estimated subject-specific effects, and these estimates were then entered into a second-level analysis with subject treated as a random effect. Beta values were used for all analyses. Whole brain group voxel-wise effects were corrected for multiple comparisons using extent thresholds at the cluster level to yield family-wise error correction and were considered significant at P < 0.05. Group level contrasts were rendered on a 3D brain using Connectome Workbench (humanconnectome.org/software/connectome-workbench).

ROI Analysis

Regions of interest (ROIs) were constructed from previous studies, complemented whole brain analyses, or were derived from a functional network parcellation. ROIs taken from a previous abstract sequence study (Desrochers et al., 2015) were defined from significant peaks of activation from the Parametric ramp model voxelwise contrast All Ramp > Baseline (referred to as Abstract Ramp > Baseline in the present study). ROIs from the original motor sequence study were defined from significant peaks of activation from t-maps decoded by classifiers (see Yewbrey et al., (2023) methods), and the anterior HPC ROIs were constructed from the AAL atlas (Rolls et al., 2020). Additional ROIs that complemented whole brain analyses were derived from significant peaks of activation from the Parametric ramp model voxelwise contrast Production Ramp > Baseline. These biased, contrast-derived ROIs were used solely for the purpose of performing a relative comparison with the unbiased, a priori-defined ROIs and were not used for independent analyses. Lastly, the network ROIs were taken from a functional network parcellation (Yeo et al., 2011). We extracted beta values from these ROIs, and repeated measures analysis of variance (RM-ANOVA) or t-tests were subsequently performed on these values.

Results

Participants performed four different pre-trained motor sequences, each of five finger presses, while undergoing fMRI scanning (Yewbrey et al., 2023). Each sequence had a different inter-press timing interval and finger order. Data in the current study were analyzed from the production phase of "Go" trials when participants performed the five finger press sequences (**Figure 1B**). Each sequence was indicated at the trial onset by a specific fractal. The cue was followed by a preparation period indicated by a white fixation cross on a black screen, and then a green screen with a centered black hand icon, which indicated to the participants to initiate the finger presses (the "go" cue). The production period of each trial was followed by a fixation period and feedback on the current trial. Participants were trained prior to the fMRI scanning session to perform the four sequences from memory when cued.

Neural

We first tested the hypothesis that significant ramping occurs in the RLPFC during motor sequence production. We modeled a parametric ramp across finger presses for each sequence to estimate ramping activity during sequence production. To assess ramping in RLPFC, we defined an ROI from a peak cluster of ramping activity in a previous study of healthy controls (Desrochers et al., 2015), hereafter referred to as the D15 ROI. Averaging across conditions, in the Production Ramp > Baseline contrast we did not observe ramping activity significantly different from zero in the D15 ROI (**Figure 2A**; t(1,23) = -1.29, p = 0.21). Therefore, we did not find evidence of RLPFC ramping activity during motor sequence production.

Since ramping during abstract sequences occurs in a network of regions beyond the RLPFC (Desrochers et al., 2015), we next tested if significant ramping occurs in other regions of the whole brain during motor sequence production. We looked at the whole brain Production Ramp > Baseline contrast and observed three significant clusters in ventromedial PFC (vmPFC) and in the inferior parietal cortex (**Figure 2B**; **Table 1**). We compared these clusters with regions of ramping observed during abstract sequences and found that these clusters did not overlap with ramping activity previously observed in the whole brain Abstract Ramp > Baseline contrast during abstract sequence execution (Desrochers et al., 2015). From these contrasts, we showed significant ramping occurred during motor sequence production in different regions than ramping during abstract sequences.

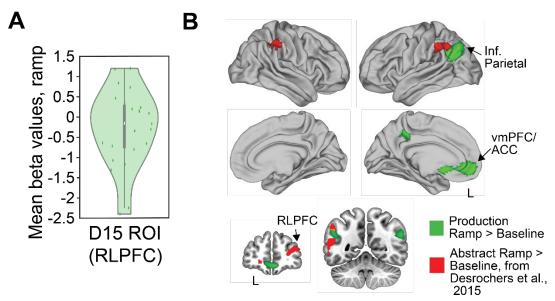


Figure 2. Ramping in RLPFC and throughout the brain during motor sequence production. A. Average ramping activity during motor sequence production is not significantly different from zero in the D15 RLPFC ROI. B. Significant ramping activity in the Abstract Ramp > Baseline contrast from Desrochers et al., (2015) shown in red, significant ramping activity in the Production Ramp > Baseline contrast in the present study. Activity shown on whole brains and in slices (FWE cluster corrected at P < 0.05, extent threshold 217 voxels for the Production Ramp > Baseline contrast and 172 voxels for the Abstract Ramp > Baseline contrast from the previous study.

To more directly test if regions of parietal ramping during motor sequences are distinct from those that ramp during abstract sequences, we conducted ROI analyses. Specifically, we compared ROIs derived from parietal clusters of activation in the Production Ramp > Baseline contrast of the current study with regions of parietal ramping in the Abstract Ramp > Baseline contrast in Desrochers et al. (2015). We note that these ROIs derived from the contrast in the current study (Production Ramp > Baseline) were biased, and therefore only used for comparison with the unbiased Abstract Ramp > Baseline clusters. Even if one region showed significant activation and the other did not, they must be directly compared to assess whether activity levels are different. To perform this comparison and for simplicity we combined the parietal Production Ramp > Baseline clusters into one ROI, which we will refer to as the 'Motor Parietal' ROI. There were four clusters of activation in the parietal cortex during abstract sequences from the Abstract Ramp > Baseline contrast in the previous study; for simplicity, we combined the two dorsal clusters and will refer to these as the 'Abstract Dorsal' ROI and the two ventral clusters, which we will refer to as the 'Abstract Ventral' ROI (Figure 3A). We compared ramping activity in the Motor Parietal with ramping in the Abstract Dorsal and Ventral ROIs in the Production Ramp > Baseline contrast to test if parietal ramping is spatially differentiated between motor and abstract sequences. We found that there was significantly increased ramping in the Motor Parietal ROI, significantly negative ramping in the Abstract Dorsal ROI, and no significant ramping in the Abstract Ventral ROI (Figure 3B; Motor Parietal: t(1,23) = 6.32, p < 0.001; Abstract Dorsal: t(1,23) = -6.94, p < 0.001; Abstract Ventral: t(1,23) = 0.34, p = 0.75; Motor Parietal x Abstract Dorsal: F(1,23) = 87.91, p < 0.001; Motor Parietal x Abstract Ventral: F(1,23) = 49.74, p < 0.001). We therefore show that increased parietal ramping during motor sequences occurs in distinct regions compared to abstract sequence parietal ramping.

As an exploratory analysis, we next investigated if the Motor Parietal ramping overlapped with other parietal regions previously observed to show different activity patterns between the motor sequences during motor sequence production (Yewbrey et al., 2023). In this study, sequence order was decoded in two right parietal cortex regions close to the Motor Parietal ROIs. We reasoned that ramping as a neural dynamic could in part be the neural activity observed in these decoding analyses. Here, we leave open what features (or their integration) is driving the decoding of sequence identity. To test this hypothesis, we created ROIs from parietal regions decoded previously from the combined and integrated classifiers (referred to as 'Decoding combined' and 'Decoding integrated' [Figure 3A]) (Yewbrey et al., 2023) and tested ramping in these ROIs compared to the right Motor Parietal ROI. We found that there is significant positive ramping in both decoded parietal ROIs compared to zero but significantly less ramping activity in these ROIs compared to the right Motor Parietal ROI (Figure 3C; Decoding combined: t(1,23) = 3.43, p = 0.002; Decoding integrated: t(1,23) = 2.78, p = 0.01; Motor Parietal x Decoding combined: F(1,23) = 21.12, p < 0.001; Motor Parietal x Decoding integrated: F(1,23) = 8.66, p = 0.007). We therefore show that ramping occurs in parietal cortex regions previously associated with motor sequence production, and these regions are also distinct from the Abstract Dorsal and Ventral parietal ROIs.

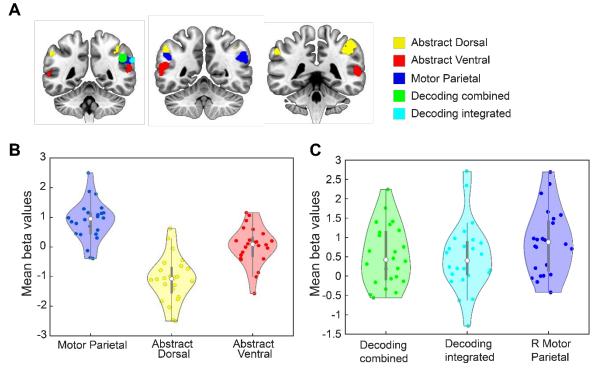


Figure 3. Parietal cortex ramping during motor sequence production. A. Abstract Ramp > Baseline activity during abstract sequences in the dorsal parietal (yellow) and ventral parietal (red) cortex. These ROIs are referred to as the 'Abstract Dorsal' and 'Abstract Ventral' ROIs. Production Ramp > Baseline activity during motor sequence production in the parietal cortex (blue), referred to as the 'Motor Parietal' ROI. Decoded activity during motor sequence production from combined (green) and integrated (cyan) conditions in the parietal cortex, referred to as the 'Decoding combined' and 'Decoding integrated' ROIs. B. Significantly greater Production Ramp > Baseline activity occurs in the Motor Parietal ROI (blue in A) compared to in the Abstract Dorsal and Ventral ROIs (yellow and red in A). C. Production Ramp > Baseline activity is significantly greater than zero in Decoding combined and integrated ROIs, but significantly less than Production Ramp > Baseline activity in the right Motor Parietal ROI.

We next investigated the connectivity and potential functional relevance of the Motor Parietal regions, motivated by the previous finding of significant ramping in the frontoparietal network (FPN) during abstract sequences (Desrochers et al., 2015). We examined ramping in two functionally distinct networks, the FPN and default mode (DMN) networks, during motor sequences. Since we observed that Motor Parietal ramping overlaps with default mode network (DMN) and not with the regions of the FPN (**Figure 4A**), we hypothesized that Motor Parietal ramping occurs primarily in the DMN compared to the FPN. We used DMN and FPN ROIs, derived as masks from a previous study (Yeo et al., 2011), to test this hypothesis. Although DMN ramping was not significantly different from zero (t(1,23) = 1.49, p = 0.15), we observed significantly more ramping in the DMN compared to the FPN, where there was negative ramping compared to zero in the Production Ramp > Baseline contrast (**Figure 4B**; FPN: t(1,23) = -4.14, p < 0.001; DMN x FPN: F(1,23) = 74.09, p < 0.001). These results together suggest that motor and abstract sequence production may be functionally separated by these two networks, with DMN activation underlying motor sequence production and positive FPN activation supporting abstract sequence processing.

To further explore networks of regions functionally relevant to motor sequence production, we investigated ramping in anterior hippocampus (HPC). We chose this region because HPC activity was shown to be decreased during motor sequence execution (Yewbrey and Kornysheva, 2024), which could be due to ramping dynamics. We found significant negative ramping in the left but not the right anterior HPC compared to zero (**Figure 4C**; L aHPC: t(1,23) = -2.41, p = 0.025; R aHPC: t(1,23) = -1.02, p = 0.32; L aHPC x R aHPC: F(1,23) = 5.53, p = 0.03), which concurs with previous findings. Ramping findings in the HPC suggest the left HPC may be functionally connected to and recruited with regions of the FPN during motor sequence production. Overall, these results provide more evidence for functionally distinct regions recruited during motor compared to abstract sequence production.

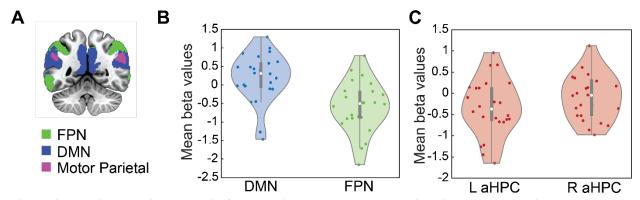


Figure 4. Negative ramping occurs in frontoparietal network and anterior hippocampus during motor sequence production. A. Whole brain representation of the frontoparietal network (FPN in green), the default mode network (DMN in blue), and significant ramping in the Production Ramp > Baseline contrast (in magenta). Ramping during motor sequence production overlaps with the DMN. B. Production Ramp > Baseline activity lies in the DMN, and there is significant negative ramping in the Production Ramp > Baseline contrast in the FPN. C. No significant Production Ramp > Baseline activity occurs in the right anterior hippocampus (HPC) but there is significant negative ramping in the left anterior HPC.

Discussion

We investigated RLPFC ramping dynamics during motor sequence production, using data from a previously published fMRI study (Yewbrey et al., 2023), with a hypothesis that RLPFC ramping dynamics generalize to track motor in addition to abstract sequence production. Contrary to this hypothesis, we did not observe significant RLPFC ramping during motor sequences, suggesting RLPFC dynamics are specific to abstract sequences. However, we found significant ramping in the vmPFC and parietal cortical regions distinct from those recruited during abstract sequences. Further, we observed negative FPN and HPC ramping activity during motor sequence production, in contrast to positive FPN ramping observed previously during abstract sequences. Overall, ramping dynamics reveal that distinct prefrontal-parietal regions and differential cortical networks support motor compared to abstract sequence production.

Since RLPFC ramping does not support motor sequence production, recruitment of this region may be specific to non-motor, such as abstract, sequences. The anterior PFC has been previously associated with hierarchical abstraction and structures (Koechlin et al., 1999, 2003; Sakai and Passingham, 2003; M et al., 2005). One theory poses a hierarchical organization of the PFC (Badre and D'Esposito, 2007), such that rostral PFC regions are recruited for more abstract facets of cognitive control. Regions caudal to PFC regions such as the motor and premotor cortex, however, are recruited during motor sequence execution (Tanji and Shima, 1994; Yokoi and Diedrichsen, 2019; Russo et al., 2020). Since the motor sequences in the present study are pre-trained and memorized prior to the fMRI scan, monitoring their execution may not be required in the same manner as for abstract sequences. Therefore, in the present behavioral paradigm, rostral PFC regions such as the RLFPC may not be necessary to help monitor the production of such sequences. More generally, RLPFC may not be recruited during skilled motor sequence production. Overall, our work provides evidence for circuitry supporting motor sequence production that is distinct from that underlying abstract sequences, implicating clinical disorders related to these sequence types.

The parietal ramping findings suggest differential cortical networks underlying motor sequence compared to abstract sequence production. Prior neuroimaging experiments have provided some evidence for the hierarchical differentiation of parietal cortex. For example, the Abstract Dorsal parietal ROI was shown previously to hold information about both higher and lower level contextual information needed to hold memory during a task (Nee and Brown, 2012). Further, the Abstract Dorsal ROI is part of the FPN and is active during task-switching (Periáñez et al., 2024), which is necessary for flexible behavior related to higher-level cognitive processing. The Motor Parietal regions were not activated in either study but are involved in more concrete aspects of sequential processing, such as number processing (Göbel et al., 2001; Grabner et al., 2009). These experiments suggest that parietal regions involved in abstract (the Abstract Dorsal and Ventral ROIs) versus motor sequences (the Motor Parietal ROI) may be differentiated by the hierarchical information they represent. In the current study, differential network dynamics, positive DMN ramping and significant negative FPN ramping during motor sequences, suggests these networks may differentiate the two sequence types as well. Distinct parietal regions and differential cortical networks may therefore support motor compared to abstract sequence production.

We observed ramping in vmPFC during motor sequences, which may be due to feedback during the task. Ramping activity occurs in anticipation of reward in the vmPFC (Lamichhane et al., 2022). During the motor sequence task, participants were provided with feedback after each

production period, which may produce ramping signals similar to those seen in reward anticipation. Therefore, it is possible that vmPFC ramping observed may be more related to feedback than to sequential information during the production period. Future studies should be designed to isolate reward as a variable to more accurately assess ramping related directly to motor sequence production.

This study was primarily limited by the task, which was not originally designed to answer the questions posed in the current study. Although the present study was able to show strong evidence for ramping during motor sequences in isolation, future experiments should directly investigate ramping in motor compared to abstract sequence production using hierarchical/nested structures (building on Yokoi et al., (2019) but extending to non-motor sequences). Lastly, we were unable to model the sequence preparation period parametrically without button press timings, so the present study focused only on motor sequence production. Future studies should directly test ramping during motor sequence preparation compared to production. Future work may also prioritize investigating the connectivity of the differentiated parietal cortical regions in abstract versus motor sequences to better determine networks that contribute to the production of each sequence type.

Our work has implications for both psychiatric disorders associated with sequential deficits, such as obsessive-compulsive disorder (OCD). Previous studies showed reaction time deficits in OCD during implicitly learned motor sequences (Kathmann et al., 2005; Kelmendi et al., 2016; Soref et al., 2018) and dysfunctional prefrontal and basal ganglia circuitry that underlie this process (Milad and Rauch, 2012; Janacsek et al., 2020). We have shown that abstract sequence execution in an OCD population is largely similar to that of healthy controls, with no difference in RLPFC activation or ramping dynamics between groups (Doyle et al., 2024). These studies suggest abstract sequential behavior observed in OCD patients may occur due to deficits in the execution of motor sequences nested within abstract sequences. Our present results extend this hypothesis to include specific prefrontal and parietal regions of ramping that may be dysfunctional in OCD during sequential behavior.

Overall, motor sequence production is supported by prefrontal-parietal circuitry and cortical networks that are distinct from regions and networks recruited during abstract sequence execution. Our results provide evidence for novel neural circuitry underlying skilled motor sequences and provide further evidence for neural differentiation of hierarchical sequence information.

<u>Data Availability:</u> Imaging data are not publicly available. Analysis code is available upon request.

<u>Author Contributions:</u> Hannah Doyle: Conceptualization, Investigation, Methodology, Formal Analysis, Writing – Original Draft, Writing – Reviewing and Editing, Visualization. Rhys Yewbrey: Data Curation, Conceptualization, Writing – Reviewing and Editing. Katja Kornysheva: Conceptualization, Validation, Writing – Reviewing and Editing, Supervision. Theresa M. Desrochers: Conceptualization, Validation, Writing – Original Draft, Writing – Reviewing and Editing, Supervision, Funding Acquisition.

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Tables

Contrast Location	BA Extent (voxels)		x	у	Z	Peak t-val.
Production Ramp > Baseline						
R ventromedial PFC	11	345	6	50	-12	6.48
L ventromedial PFC	11		-8	42	-12	4.75
Anterior cingulate gyrus	11		6	34	-10	4.32
R angular gyrus	40	265	54	-50	30	5.91
L angular gyrus	39	517	-44	-72	32	6.9
L angular gyrus	39		-50	-58	28	5.92

Table 1. Activation coordinates, significant neural activity in the Production Ramp > Baseline contrast. Clusters reliable at p < 0.05 corrected. Coordinates are the center of mass in MNI. Clusters are reported for peaks of activation 8 mm or greater distance apart.

References

- Ariani G, Pruszynski JA, Diedrichsen J (2022) Motor planning brings human primary somatosensory cortex into action-specific preparatory states Baker CI, Serino A, Kikkert S, eds. eLife 11:e69517.
- Badre D, D'Esposito M (2007) Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. J Cogn Neurosci 19:2082–2099.
- Desrochers TM, Ahuja A, Maechler MR, Shires J, Yusif Rodriguez N, Berryhill ME (2022) Caught in the ACTS: Defining Abstract Cognitive Task Sequences as an Independent Process. Journal of Cognitive Neuroscience 34:1103–1113.
- Desrochers TM, Chatham CH, Badre D (2015) The Necessity of Rostrolateral Prefrontal Cortex for Higher-Level Sequential Behavior. Neuron 87:1357–1368.
- Desrochers TM, Collins AGE, Badre D (2019) Sequential Control Underlies Robust Ramping Dynamics in the Rostrolateral Prefrontal Cortex. J Neurosci 39:1471–1483.
- Doyle H, Garnaat S, McLaughlin N, Desrochers TM (2024) Cognitive sequences in obsessive-compulsive disorder are supported by frontal cortex ramping activity and mediated by symptom severity. :2024.07.28.605508 Available at: https://www.biorxiv.org/content/10.1101/2024.07.28.605508v2 [Accessed October 8, 2024].
- Göbel S, Walsh V, Rushworth MF (2001) The mental number line and the human angular gyrus. Neuroimage 14:1278–1289.
- Grabner RH, Ansari D, Koschutnig K, Reishofer G, Ebner F, Neuper C (2009) To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia 47:604–608.
- Hikosaka O, Nakamura K, Sakai K, Nakahara H (2002) Central mechanisms of motor skill learning. Current Opinion in Neurobiology 12:217–222.
- Janacsek K, Shattuck KF, Tagarelli KM, Lum JAG, Turkeltaub PE, Ullman MT (2020) Sequence learning in the human brain: A functional neuroanatomical meta-analysis of serial reaction time studies. Neuroimage 207:116387.
- Kathmann N, Rupertseder C, Hauke W, Zaudig M (2005) Implicit sequence learning in obsessive-compulsive disorder: further support for the fronto-striatal dysfunction model. Biol Psychiatry 58:239–244.
- Kelmendi B, Adams T, Jakubovski E, Hawkins KA, Coric V, Pittenger C (2016) Probing Implicit Learning in Obsessive-Compulsive Disorder: Moderating Role of Medication on the Weather Prediction Task. J Obsessive Compuls Relat Disord 9:90–95.

- Koechlin E, Basso G, Pietrini P, Panzer S, Grafman J (1999) The role of the anterior prefrontal cortex in human cognition. Nature 399:148–151.
- Koechlin E, Ody C, Kouneiher F (2003) The architecture of cognitive control in the human prefrontal cortex. Science 302:1181–1185.
- Lamichhane B, Di Rosa E, Braver TS (2022) Delay of gratification dissociates cognitive control and valuation brain regions in healthy young adults. Neuropsychologia 173:108303.
- M B, M U, Tr K, Dy von C, Na P (2005) Who comes first? The role of the prefrontal and parietal cortex in cognitive control. Journal of cognitive neuroscience 17 Available at: https://pubmed.ncbi.nlm.nih.gov/16197690/ [Accessed October 8, 2024].
- Milad MR, Rauch SL (2012) Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci 16:43–51.
- Nee DE, Brown JW (2012) Rostral-Caudal Gradients of Abstraction Revealed by Multi-Variate Pattern Analysis of Working Memory. Neuroimage 63:1285–1294.
- Periáñez JA, Viejo-Sobera R, Lubrini G, Álvarez-Linera J, Rodríguez Toscano E, Moreno MD, Arango C, Redolar-Ripoll D, Muñoz Marrón E, Ríos-Lago M (2024) New functional dissociations between prefrontal and parietal cortex during task switching: A combined fMRI and TMS study. Cortex 179:91–102.
- Rolls ET, Huang C-C, Lin C-P, Feng J, Joliot M (2020) Automated anatomical labelling atlas 3. NeuroImage 206:116189.
- Rosenbaum DA, Cohen RG, Jax SA, Weiss DJ, van der Wel R (2007) The problem of serial order in behavior: Lashley's legacy. Human Movement Science 26:525–554.
- Russo AA, Khajeh R, Bittner SR, Perkins SM, Cunningham JP, Abbott LF, Churchland MM (2020) Neural Trajectories in the Supplementary Motor Area and Motor Cortex Exhibit Distinct Geometries, Compatible with Different Classes of Computation. Neuron 107:745-758.e6.
- Sakai K, Passingham RE (2003) Prefrontal interactions reflect future task operations. Nat Neurosci 6:75–81.
- Soref A, Liberman N, Abramovitch A, Dar R (2018) Explicit instructions facilitate performance of OCD participants but impair performance of non-OCD participants on a serial reaction time task. Journal of Anxiety Disorders 55:56–62.
- Tanji J, Shima K (1994) Role for supplementary motor area cells in planning several movements ahead. Nature 371:413–416.
- Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL (2011) The

- organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106:1125–1165.
- Yewbrey R, Kornysheva K (2024) The hippocampus pre-orders movements for skilled action sequences. J Neurosci Available at: https://www.jneurosci.org/content/early/2024/09/23/JNEUROSCI.0832-24.2024 [Accessed October 8, 2024].
- Yewbrey R, Mantziara M, Kornysheva K (2023) Cortical Patterns Shift from Sequence Feature Separation during Planning to Integration during Motor Execution. J Neurosci 43:1742–1756.
- Yokoi A, Arbuckle SA, Diedrichsen J (2018) The Role of Human Primary Motor Cortex in the Production of Skilled Finger Sequences. J Neurosci 38:1430–1442.
- Yokoi A, Diedrichsen J (2019) Neural Organization of Hierarchical Motor Sequence Representations in the Human Neocortex. Neuron 103:1178-1190.e7.
- Zimnik AJ, Churchland MM (2021) Independent generation of sequence elements by motor cortex. Nat Neurosci 24:412–424.