Monkey dorsolateral prefrontal cortex represents abstract visual sequences during a no-report task

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Abstract

Monitoring sequential information is an essential component of our daily lives. Many of these sequences are abstract, in that they do not depend on the individual stimuli, but do depend on an ordered set of rules (e.g., chop then stir when cooking). Despite the ubiquity and utility of abstract sequential monitoring, little is known about its neural mechanisms. Human rostrolateral prefrontal cortex (RLPFC) exhibits specific increases in neural activity (i.e., "ramping") during abstract sequences. Monkey dorsolateral prefrontal cortex (DLPFC) has been shown to represent sequential information in motor (not abstract) sequence tasks, and contains a sub-region, area 46, with homologous functional connectivity to human RLPFC. To test the prediction that area 46 may represent abstract sequence information, and do so with parallel dynamics to those found in humans, we conducted functional magnetic resonance imaging (fMRI) in monkeys. When monkeys performed no-report abstract sequence viewing, we found that left and right area 46 responded to abstract sequential changes. Interestingly, responses to rule and number changes overlapped in right area 46 and left area 46 exhibited responses to abstract sequence rules with changes in ramping activation, similar to that observed in humans. Together, these results indicate that monkey DLPFC monitors abstract visual sequential information, potentially with a preference for different dynamics in the two hemispheres. More generally, these results show that abstract sequences are represented in functionally homologous regions across monkeys and humans.

60 **Significance Statement**

61 Daily, we complete sequences that are "abstract" because they depend on an ordered set of rules
62 (e.g., chop then stir when cooking) rather than the identity of individual items. Little is known
63 about how the brain tracks, or monitors, this abstract sequential information. Based on previous
64 human work showing abstract sequence related dynamics in an analogous area, we tested if
65 monkey dorsolateral prefrontal cortex (DLPFC), specifically area 46, represents abstract
66 sequential information using awake monkey fMRI. We found that area 46 responded to abstract
67 sequence changes, with a preference for more general responses on the right and dynamics
68 similar to humans on the left. These results suggest that abstract sequences are represented in
69 functionally homologous regions across monkeys and humans.

Introduction

Sequential tasks that require monitoring are prevalent in daily life. For example, taking a bus requires tracking familiar sequences of buildings (e.g., three houses then a library), enabling the detection of deviations from this sequence (e.g., if there is a detour). Similarly, many cognitive processes occur serially, and often demand that we maintain an internal representation of the previous steps to complete the next. Even in tasks that are not explicitly sequential, a system for tracking transitions between steps, such as when completing a mathematical operation, may be essential.

Sequence monitoring is this active process of tracking the order of subsequent "states" or steps. Monitoring is distinct from other well-studied sequence processes, such as explicit memorization, or potentially more automatic behaviors, such as a series of motor outputs (e.g., playing the piano) or statistical sequence learning (Desrochers et al., 2019) . Such sequential processes likely contain monitoring operations within them but are also comprised of other cognitive computations. *Abstract sequences* are sequences that are not dependent on the individual stimuli but can instead be described by the rule they follow (e.g., three same, one different or AAAB) (Desrochers et al., 2022). Therefore, *abstract sequence monitoring* entails sequences of sensory stimuli that possess abstract structure and active monitoring of this structure. While it may be assumed that abstract sequence monitoring underlies many aforementioned sequence types (including motor sequences), it is rarely studied in isolation and the neural underpinnings of abstract sequence monitoring remain largely unknown.

Multiple modes of evidence in humans indicate that activity in rostrolateral prefrontal cortex (RLPFC) is crucial to sequence monitoring (Desrochers et al., 2015, 2019; McKim and

Desrochers, 2022). Functional magnetic resonance imaging (fMRI) revealed systematic increasing activity ("ramping") from the beginning to the end of each sequence in human RLPFC. Across studies, this activity occurs either bilaterally, or in the left RLPFC. Further, noninvasive transcranial magnetic stimulation (TMS) showed that the left RLPFC was necessary for sequential tasks in humans. Other studies have also demonstrated the involvement of RLPFC as part of a frontoparietal network active during complex sequential tasks (Farooqui et al., 2012; Wang et al., 2019; Wen et al., 2020). While consistent with the findings discussed above, these studies frequently involve other cognitive phenomena, like decision-making, leaving open their specific role of sequence monitoring.

Studies in nonhuman primates also suggest a role of lateral prefrontal cortex in abstract visual sequence monitoring. Motor sequence studies show that neurons in the dorsolateral prefrontal cortex (DLPFC) are selective for serial position (Barone and Joseph, 1989; Averbeck et al., 2006; Shima et al., 2007; Berdyyeva and Olson, 2010) and sequence boundaries (Fujii and Graybiel, 2003), and include neural dynamics that could underlie the ramping observed in human BOLD activation(Desrochers et al., 2015, 2019; McKim and Desrochers, 2022). Neurons in the DLPFC also show ordinal selectivity during visual object sequences (Ninokura et al., 2004; Warden and Miller, 2010; Naya et al., 2017). A rich literature also supports the involvement of DLPFC in representing non-sequential abstract rules (Hoshi et al., 1998; White and Wise, 1999; Wallis et al., 2001; Eiselt and Nieder, 2013). Responses in the DLPFC can also selectively represent sequential regularities (Vergnieux and Vogels, 2020). Together, these physiological studies suggest that the monkey DLPFC is well-positioned to monitor abstract visual sequences.

113 We hypothesized that a specific sub-region of monkey DLPFC (area 46) monitors visual abstract
114 sequential information. In humans, abstract sequence monitoring has been localized to the
115 RLPFC, which is distinct from the rostromedial prefrontal cortex (Koechlin et al., 2000; Burgess
116 et al., 2003; Gilbert et al., 2010; Moayedi et al., 2015; Henssen et al., 2016; Du et al., 2020).
117 While rostromedial prefrontal cortex has similar connectivity in monkeys and humans,
118 anatomical evidence suggests that monkey area 46 contains the most similar connectivity
119 patterns to human RLPFC (Sallet et al., 2013; Neubert et al., 2014), and overlapping high-level
120 visual representations (Xu et al., 2022). Therefore, we predicted that abstract visual sequence
121 monitoring would be supported by monkey area 46, and that similar ramping dynamics, as
122 observed in humans, would localize to this same area.

123 To directly test these predictions, we conducted event-related fMRI in awake nonhuman
124 primates, and used deviations from established abstract visual sequences during a no-report task
125 to index abstract sequence monitoring. We found that nonhuman primate DLPFC distinctly
126 represents abstract visual sequence information, independent from other task constraints.
127 Additionally, we find that these abstract sequences elicit ramping dynamics similar to those
128 observed in humans during abstract sequence performance. Intriguingly, deviant responses with
129 differing primary dynamics were observed in the two hemispheres: an onset-based signal on the
130 right, and ramping on the left. These findings indicate that a specific sub-region of DLPFC
131 preferentially supports abstract sequence monitoring in monkeys and may be functionally
132 homologous to humans. Further, these results establish an important connection between human
133 and monkey complex cognition and the neural substrates that mediate it, providing a foundation
134 for understanding more complex behaviors across species in the future.

Materials and Methods

Subjects

We tested three adult male rhesus macaques (ages spanning 6-12 years during data collection, 9-14 kg). All procedures followed the NIH Guide for Care and Use of Laboratory Animals and were approved by Institutional Animal Care and Use Committee (IACUC) at Brown University.

No-Report Abstract Visual Sequence Task

All visual stimuli used in this study were displayed using an OpenGL-based software system developed by Dr. David Sheinberg at Brown University. The experimental task was controlled by a QNX real-time operating system using a state machine. Eye position was monitored using video eye tracking (Eyelink 1000, SR Research). Stimuli were displayed at the scanner on a 24-inch BOLDscreen flat-panel display (Cambridge Systems). The general design of the visual sequence paradigm was based on a similar auditory sequence task (Wang et al., 2015).

Stimuli

Each image presentation consisted of fractal stimulus (approximately 8° visual angle) with varying colors and features. Fractals were generated using MATLAB for each scanning session using custom scripts based on stimuli from (Kim and Hikosaka, 2013) following the instructions outlined in (Miyashita et al., 1991). For each scan session, new, luminance matched, fractal sets were generated. All stimuli were presented on a gray background, with a fixation spot that was always present on the screen superimposed on the images. To provide behavioral feedback, the fixation spot was yellow when the monkey was successfully maintaining fixation and red if the monkey was not fixating. Stimuli were displayed for 0.1 to 0.3 s each, depending on the sequence type and timing template, detailed as follows.

Sequence Types

There are five sequence types in this task (**Figure 1**): habituation sequences and four deviant sequence types. Across these sequence types, there were a total of nine different timing templates used. These templates were included to counterbalance for stimulus and sequence duration across the sequence types and to provide a greater variety of sequential timings during habituation. The inter-sequence interval was jittered to decorrelate across timing templates (mean 2 s, 0.25-8 s).

Habituation Sequences

Habituation sequences were composed of images drawn from a pool of four possible fractals. We will refer to the habituation image pool as [A, B, C, D]. Sequences were composed from these images in one of two possible rules: three the same, one different (e.g., AAAB, DDDC) and four the same (e.g., AAAA, CCCC). All sequences contained four images and followed one of three possible general timings based on the total duration of the sequence: short (1.1 s), medium (1.7 s), and long (2.3 s). Each total sequence duration, in turn, had two possible timing templates within it, one with longer stimulus durations and one with shorter stimulus durations: short 0.1 s and 0.2 s, medium 0.1 s and 0.3 s, long 0.2 s and 0.3 s. Inter-stimulus intervals were arranged to evenly space the four stimulus presentations within the total sequence duration.

Deviant Sequences

Deviant sequences were composed of images drawn from a different pool of three possible fractals. We will refer to the deviant image pool as [E, F, G]. All deviant images were displayed for 0.2 s, regardless of deviant type. Across deviant types, the total sequence durations were

matched to the short, medium, and long habituation timing templates. There were four deviant types, detailed as follows:

New Items, Same Rule (NISR): These deviants use images that come from the deviant pool of images, but do not differ from the habituation rule. For example, if the habituation rule was three the same, one different then NISR sequences would follow the same rule with new images (e.g., GGGF and FFFE) Alternatively, if the habituation rule was four same, an example NISR would be EEEE. All sequences were four items and had a total duration of 1.7 s.

Rule deviants: These deviants do not follow the same rule as habituation, but instead follow the alternate rule. If the habituation rule was three the same, one different, example deviants would follow the four the same rule, e.g., EEEE and GGGG. All deviants contained four images and had a total sequence duration of 1.7 s, the same as medium habituation sequences.

Number Deviants: These deviants follow the same rule as habituation but contain a different number of images (either two or six). If the habituation rule was three the same, one different, example deviants would be EG and FFFFFE. Two-item deviants had a total sequence duration of 1.1 s, the same as short habituation sequences, and six-item deviants had a total sequence duration of 2.3 s, the same as long habituation sequences.

Double Deviants: These deviants combine Rule and Number deviant types. If the habituation rule was three the same, one different, example deviants would be EE and GGGGGG. The timing was the same as number deviants.

Block Structure

Each block contained 30 sequences and lasted approximately 112 s on average. Habituation blocks contained equal numbers of the six possible timing templates (two of each: short, medium, and long). Habituation sequences were presented in pseudo-random order such that a sequence could not begin with the same fractal as the final fractal of the previous sequence. Deviant blocks were composed of 24 habituation sequences and six deviant sequences. All deviant sequences within a block were of the same sequence type. The six deviant sequences were pseudo-randomly interspersed throughout the block such that deviant sequences did not occur in the first 6 sequences of the block (to avoid block initiation confounds), and deviant sequences were not presented consecutively to each other. If deviant sequences contained a variable number of items (i.e., number deviants and double deviants), then an equal number of two- and six-item sequences were included within a single block. The 24 habituation sequences within deviant blocks were presented in the same manner as in habituation blocks (i.e., evenly distributed timing templates and avoiding between-sequence fractal image repeats).

Run Structure

Each run was composed of five blocks, interleaved with 14 s fixation blocks (**Figure 1**). The first block of each run contained only habituation sequences. The four subsequent blocks were one of each of the four possible deviant types, with their order counterbalanced across runs. The same habituation rule was used for the entirety of a single run. Runs lasted approximately 10.5 min. The sequence rule (*three same, one different* or *four same*) used for each run was counterbalanced across each scanning session so as to have an equal number of runs for each rule. Monkeys typically completed 4-8 runs of this task (among other tasks not reported on here) in a single scanning session (one day).

220 Runs were initiated according to the monkey's fixation behavior to ensure that the monkey was
221 not moving and engaged in the task before acquiring functional images. During this pre-scan
222 period, a fixation spot was presented. Once the monkey successfully acquired this fixation spot
223 and received approximately four liquid rewards (12 – 16 s), functional image acquisition and the
224 first habituation block were initiated.

225 Reward

226 The timing of liquid rewards was not contingent upon sequential events, only on the monkey
227 maintaining fixation. Rewards were delivered on a graduated schedule such that the longer the
228 monkey maintained fixation, the more frequent rewards were administered (Leite et al., 2002).
229 The first reward was given after 4 s of continuous fixation. After two consecutive rewards of the
230 same fixation duration, the fixation duration required to obtain reward was decreased by 0.5 s.
231 The minimum duration between rewards that the monkey could obtain was 0.5 s. Fixation had to
232 be maintained within a small window (typically 3° of visual angle) around the fixation spot to
233 not break fixation. The only exception was a brief time window (0.32 s) provided for blinks. If
234 the monkey's eyes left the fixation window and returned within that time window, it would not
235 trigger a fixation break. If fixation was broken, the reward schedule would restart at the
236 maximum 4 s duration required to obtain reward.

237 **FMRI Data Acquisition**

238 Monkeys were trained to sit in the "sphynx" position in a custom MR-safe primate chair
239 (Applied Prototype, Franklin, MA or custom-made by Brown University). The monkey's head
240 was restrained from moving via a plastic "post" (PEEK, Applied Prototype, Franklin, MA)
241 affixed to the monkeys' head and the primate chair. Monkeys were habituated to contrast agent

242 injection procedures, recorded MRI sounds, wearing earplugs (Mack's Soft Moldable Silicone
243 Putty Ear Plugs, Kid's size), and transportation to the scanner prior to MRI scanning sessions.
244 Monkeys were trained on the behavioral task with different images that were never used during
245 scanning.

246 Prior to each scanning session, monkeys were intravenously injected with a contrast agent:
247 monocrystalline iron oxide nanoparticle (MION, Feraheme (ferumoxytol), AMAG
248 Pharmaceuticals, Inc., Waltham, MA, 30 mg per mL or BioPal Molday ION, Biophysics Assay
249 Lab Inc., Worcester, MA, 30 mg per mL). MION to improves the contrast-to-noise ratio ~3-fold
250 (Vanduffel et al., 2001; Leite et al., 2002) and enhances spatial selectivity of MR signal changes
251 (Zhao et al., 2006). MION was injected, approximately 30-60 min before scanning, into the
252 saphenous vein below the knee (7 mg/kg), then flushed with a volume of sterile saline
253 approximately double the volume of the MION injected. No additional MION was added during
254 scanning, as MION has a long blood half-life (15.3 +/- 3.5 hr) (Leite et al., 2002).

255 A Siemens 3T PRISMA MRI system with a custom six-channel surface coil (ScanMed, Omaha,
256 NE) at the Brown University MRI Research Facility was used for whole-brain imaging.
257 Anatomical scans consisted of a T1-MPRAGE (repetition time, TR, 2700 ms; echo time, TE,
258 3.16 ms; flip angle, 9°; 208 sagittal slices; 0.5 x 0.5 x 0.5 mm), a T2 anatomical (TR, 3200 ms;
259 TE 410 ms; variable flip angle; 192 interleaved transversal slices; 0.4 x 0.4 x 0.4 mm), and an
260 additional high resolution T2 anatomical (TR, 8020 ms; TE 44 ms; flip angle, 122°; 30
261 interleaved transversal slices; 0.4 x 0.4 x 1.2 mm). Functional images were acquired using a fat-
262 saturated gradient-echoplanar sequence (TR, 1.8 s; TE, 15 ms; flip angle, 80°; 40 interleaved
263 axial slices; 1.1 x 1.1 x 1.1 mm).

264 The target sample size (number of runs per monkey) was calculated using pilot data from a
265 previous version of this task not included in the current data set. A region of interest was
266 constructed from a cluster of deviant > NISR activation and the number of runs calculated for a
267 significant effect in this region (using the beta values of the onset GLM, see below) at 80%
268 power and alpha = 0.05 (G-Power). Guided by this power analysis and similar studies (Wang et
269 al., 2015), we estimated a total of 200 runs across the three animals would be necessary.

270 **FMRI Data Analysis**

271 The majority of the following analyses were performed in Matlab using SPM 12 (http://www.fil.
272 Ion.ucl.ac.uk/spm). Prior to analysis, data were preprocessed using the following steps:
273 reorienting (to ensure proper assignment of the x,y,z planes), motion correction (realignment),
274 normalization, and spatial smoothing (2 mm isotropic Gaussian kernel separately for gray matter
275 and white matter). All steps were performed on individual runs separately. The T1-MPRAGE
276 anatomical image was skull stripped using FSL BET brain extraction tool
277 (http://www.fmrib.ox.ac.uk/fsl/) to facilitate normalization. All images were normalized to the
278 112-RM SL macaque atlas (McLaren et al., 2009).

279 Runs were included for analysis only if they met the following criteria: the monkey had to be
280 performing well and a sufficient number of acquisition volumes within the run had to pass data
281 quality checks. The monkey's performance was evaluated by calculating the percentage of time
282 within a run that fixation was maintained. Runs were excluded if the monkey was fixating < 80%
283 of the time (similar criteria as in (Vanduffel et al., 2001; Leite et al., 2002; Wang et al., 2015).
284 Approximately 20% of runs were excluded due to poor fixation: 10% from monkey J, 3% from
285 monkey W and 7% from monkey B. To evaluate data quality, we used the ART toolbox (Artifact

Detection Tools, https://www.nitrc.org/projects/artifact_detect) to detect outlier volumes. Any volumes that had motion greater than one voxel (1.1 mm) in any direction were excluded. Any run with greater than 12% of volumes excluded was excluded from analysis (0% runs excluded for monkey J, 0.5% of runs excluded for monkey W, and 15% of runs excluded for monkey B). Runs with poor image quality due to artifact or banding to pre-process or analyze were also excluded. These accounted for 2% of the data for monkey J, 5% for monkey W, and 0.5% for monkey B. After applying these criteria, a total of 232 runs (average of 340 volumes per run for all animals, 93 sessions in total across animals) were included for analysis from 3 monkeys: monkey W: 97 runs (32 sessions); monkey J: 65 runs (32 sessions), and monkey B: 70 runs (32 sessions).

Models

Within-subject statistical models were constructed under the assumptions of the general linear model (GLM) in SPM 12 for each pseudo-subject bin. For all models, data were binned into approximately 10-run pseudo-subject bins. Each bin contained data from only one monkey. Runs were pseudo-randomly assigned to bins to balance the number of runs which followed each of the two sequential rules (three same one different or four same) and the distribution of runs from earlier and later scanning sessions. Condition regressors were all convolved with a gamma function (shape parameter = 1.55, scale parameter = 0.022727) to model the MION hemodynamic response function (Vanduffel and Farivar, 2014). The first six sequences in a run and reward times were included as nuisance conditions. Additional nuisance regressors were included for the six motion estimate parameters (translation and rotation), outlier volumes, and image variability (standard deviation of within run image movement variability, calculated using the ART toolbox). Outlier volumes were determined using the ART toolbox (standard global

mean; global signal detection outlier detection threshold = 4.5; motion threshold = 1.1mm; scan to scan motion and global signal change for outlier detection) and one additional regressor with a "1" at only that volume was included for each volume to be "scrubbed".

Regressors were estimated using a bin-specific fixed-effects model. Whole-brain estimates of bin-specific effects were entered into second-level analyses that treated bin as a random effect. One-sample t-tests (contrast value vs zero, $p < 0.005$) were used to assess significance. These effects were corrected for multiple comparisons when examining whole-brain group voxelwise effects using extent thresholds at the cluster level to yield false discovery rate (FDR) error correction ($p < 0.05$). Group contrasts were rendered on an inflated MNI canonical brain using Caret (Van Essen et al., 2001). Prior to selecting GLM's we used the model assessment, comparison, and selection toolbox (MACS, https://github.com/JoramSoch/MACS, (Soch and Allefeld, 2018) to determine models that would be the best fit. Three GLMs were applied to the data as follows:

Onsets Model: To assess the univariate effects of deviant sequences, we constructed a model using instantaneous stimulus onset regressors for the first item in each sequence with the following nine condition regressors for different sequence types: short, medium, and long habituation sequence timing templates; NISR; rule deviants; two- and six-item number deviants; and two- and six-item rule and number deviants.

Parametric Last Item versus Unique Ramp Model: To directly test whether variance could be better accounted for by a phasic response at the last item in the sequence or ramping activation, we constructed a pair of models to allow last item and ramp regressors to compete for variance within the same model. Onset regressors were constructed with an instantaneous stimulus onset

regressor at each position in the sequence with the same nine condition regressors for the different sequence types as in the Onsets Model: short, medium, and long habituation sequence timing templates; NISR; rule deviants; two- and six-item number deviants; and two- and six-item rule and number deviants. Including an onset at each position effectively modeled sustained activation throughout the sequence and enabled the inclusion of the following parametric regressors. The last item parametric was added as ones at the first sequence positions and an arbitrarily larger value (6) at the last item. The ramp parametric was entered as the sequence position (1-4, 1-2, or 1-6) for each sequence. Parametric regressors were implemented hierarchically in the GLM. Therefore, variance explained by the last parametric regressor (in this case, ramping), is above and beyond what could be explained by the onsets or last item regressors.

Parametric Ramp versus Unique Last Item Model: This second model of the pair sought to identify variance uniquely explained by the last item regressor, above and beyond variance explained by the onsets or ramping regressors. All other aspects of the model were the same as the unique ramp model above.

ROI Analyses

The primary bilateral regions of interest were constructed from the coordinates of a seed region centered in macaque monkey area 46d. These coordinates were determined, using diffusion weighted and functional MRI, to be most similar to the lateral portion of human area 10 (Gilbert et al., 2010; Sallet et al., 2013). Human lateral area 10 overlaps with areas of ramping activation observed in human RLPFC in previous studies (Desrochers et al., 2015, 2019; McKim and Desrochers, 2022). A 5 mm sphere was created around the center coordinate for the seed region

in macaque Montreal Neurological Institute (MNI) space. The sphere was then transformed into 112RM-SL space using RheMap (Sirmpilatze & Klink, 2020, resulting in a sphere centered at *xyz* = 12.7, 32.6, 22.5 in 112RM-SL space. For identification of brain areas we also utilized the NIMH Macaque Template (NMT v02, Macaque Atlas, Jung et al., 2021; Seidlitz et al., 2018).

Additional ROIs were constructed with the explicit purpose of comparing nearby regions in DLPFC that were significant clusters of activation last item versus ramping models. Specifically, the significant left DLPFC cluster of activation for Unique Ramp, Rule Deviants > NISR in the unique ramp model (center *xyz* = -12.2, 36, 23) and the significant left DLPFC cluster of activation for Unique Last, Rule Deviants > NISR in the unique last item model (center *xyz* = -12.3, 42.9, 21.8) were taken for comparison.

To compare activation within and across ROIs in a manner that controlled for variance, we extracted t-values from the condition of interest over baseline using the Marsbar toolbox (Jean-Baptiste Poline, 2002). T-values (one for each pseudo-subject bin, n = 22 bins) were entered into RM-ANOVAs with the identity of the monkey entered as a covariate.

Results

Three monkeys (*macaca mulatta*) performed no-report abstract sequence viewing while undergoing awake fMRI scanning. The monkeys were trained to fixate on a central spot while viewing a stream of fractal images arranged into four-item visual sequences (based on Wang, et al., **Figure 1**). This task did not require responses, only fixation, and thus was termed "no-report". The task was performed in runs (~10 min each), that each contained five blocks. For each run, the first block habituated animals to one of two possible sequential rules AAAB, or AAAA (A and B represent different images drawn from a pool of four possible images; 30

sequences in total per block). Habituation sequences each had one of six possible timing templates to balance stimulus and sequence durations across sequence types. Each subsequent block contained rare deviants (6 of the 30 sequence repetitions per block) of one of the following four possible types: new images following the same rule, number deviants (2 or 6 items), rule deviants (e.g., AAAA), or double deviants. All deviant images were drawn from a separate three-image pool. The five total blocks were interleaved with 16 s fixation blocks. To encourage animals to maintain fixation throughout, reward was administered on a graduated schedule not correlated with sequence presentation: the longer they maintained fixation, the shorter the duration between rewards. Reward was thus decorrelated from the four-item visual sequences. A total of 232 runs were analyzed (97 monkey W, 65 monkey J, 70 monkey B). Monkeys performed the task well and fixated for 95% of the time in included runs (see Methods for those excluded).

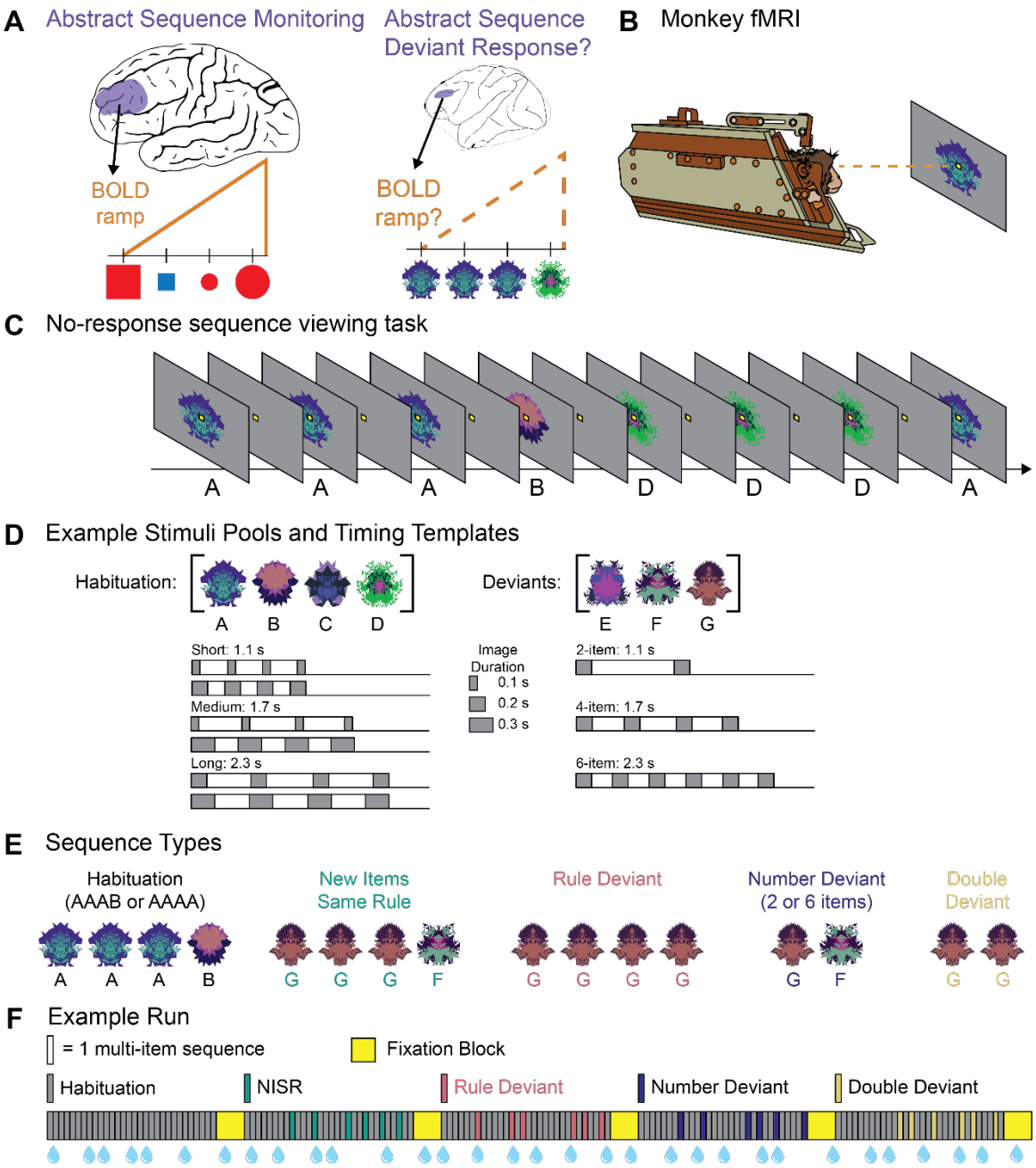


Figure 1. No-report abstract sequence viewing task. A. Schematic representation of human rostrolateral prefrontal cortex (RLPFC; left) and monkey dorsolateral prefrontal cortex (DLPFC; right) depicting the main questions that were the focus of this study: Does monkey DLPFC monitor abstract sequences, as shown by responses to deviant sequences? and does monkey DLPFC exhibit ramping activation, as found in human RLPFC during sequence monitoring? **B.** Monkeys only fixate throughout runs. Scanning is performed in the "sphynx" position. **C.** Example partial habituation block for sequence rule *three same, one different* (AAAB). **D.** Example

394 stimulus pools (top) show a set of images that would be used in a single scanning session. New images are used each
395 session. Six possible timing templates for habituation sequences (bottom, left) and deviant sequences (bottom, right)
396 illustrated with gray rectangles indicating single images. Total sequence durations are listed for each template type.
397 **E.** Examples of the five sequence types if the sequence rule in use is *three same, one different*. **F.** Example run, with
398 each bar indicating one multi-image sequence: four images in habituation, new items same rule (NISR), and rule
399 deviants; two or six images in number and double deviants. The first block contains only habituation sequences and
400 subsequent blocks contain only one of the four deviant types. Sequence blocks alternate with fixation blocks. Blue
401 water droplets schematize reward delivery, which is decoupled from sequence viewing and delivered on a graduated
402 schedule based on the duration the monkey has maintained fixation.

403 **Monkey DLPFC represents changes in abstract visual sequences**

404 Our first goal was to test whether area 46 differentially responds when there is a change in the
405 abstract visual sequence. Because this task is no-report, we examined this question using neural
406 responses (BOLD) to deviant sequences. Previous work has shown that such deviant responses
407 disappear with inattention and are robust in brain areas processing sequence related information
408 (Bekinschtein et al., 2009; Dehaene et al., 2015). These results suggest that deviant neural
409 responses indicate that individuals are attending to the sequences, even in the absence of a report.
410 Therefore, we used neural responses to rare deviant sequences to indicate awareness of changes
411 to an established abstract sequence, as is in similar auditory tasks (Uhrig et al., 2014; Wang et
412 al., 2015). To specifically query the responses to abstract sequence changes, we could not simply
413 compare habituated sequences to deviant sequences, as the deviant sequences were composed
414 from a different pool of images than the habituation sequences, and any differences observed
415 between habituation and deviant sequences could have resulted from differences in image
416 identity. Therefore, to specifically examine changes in abstract sequence structure, we compared
417 new items of the same rule (NISR) to number deviants and rule deviants. All images in this

comparison were drawn from the same pool of (deviant) images. Double deviants were not included in analyses because of the inability to dissociate between changes due to rule and number.

We first constructed an unbiased region of interest (ROI) for monkey area 46 in each hemisphere to compare activity between rule and number deviants and NISR. Monkey area 46 has many potential functional subdivisions (Gerbella et al., 2010, 2013; Borra et al., 2011, 2019; Saleem et al., 2014); therefore, we created a 5 mm sphere centered on a seed region identified as having the most similar connectivity with human RLPFC in monkey diffusion and functional MRI (Sallet et al., 2013, center *xyz* = 12.7, 32.6, 22.5 in area 46d, see Methods). The resulting sphere spanned a small region of area 46 that encompassed 46d, 46f, and 46v (NIMH Macaque Template, NMT v2.0 Macaque Atlas, Jung et al., 2021; Seidlitz et al., 2018). Because sequence related activity in human RLPFC was observed in both hemispheres, we used identical spheres (mirrored coordinates) in the left and right hemispheres (referred to as L46 and R46, respectively) throughout. To compare activity between rule and number deviants and NISR in these ROIs, we created a model that included separate regressors for each habituation timing and deviant type, modeled as zero-duration onsets. Statistical testing was performed on ~10 run bins (n = 22), each consisting of data from a single monkey (see Methods). We compared t-values from the contrast of each condition over baseline (e.g., Rule Deviants > Baseline vs. NISR > Baseline) to account for potential differences in variance across conditions. This type of comparison was used to examine ROI activity throughout, and we refer to comparisons by the conditions of interest (without listing the contrast over baseline, e.g., Rule Deviants > NISR). All statistical tests on ROIs were performed on binned data and included a covariate for monkey identity (n = 3). While

we report the effect of monkey in the following analyses, the main focus of the study was not on individual differences, and our discussion focuses on condition effects.

We found that R46 represented abstract sequence changes, showing greater deviant activation across both deviant types (**Figure 2**;**Table 1**). Responses were reliably greater for rule deviants compared to NISR (sequence type: $F(1, 19) = 4.6$, $p = 0.046$, $\eta_p^2 = 0.19$) and marginally greater for number deviants compared to NISR (sequence type: $F(1, 19) = 3.9$, $p = 0.062$, $\eta_p^2 = 0.17$). Even though deviant responses compared to NISR in L46 did not reach statistical significance (**Table 1**), there were no reliable differences between responses in R46 and L46 (**Table 2**). These results suggest that a specific region of monkey DLPFC, area 46, monitors abstract visual sequence structure.

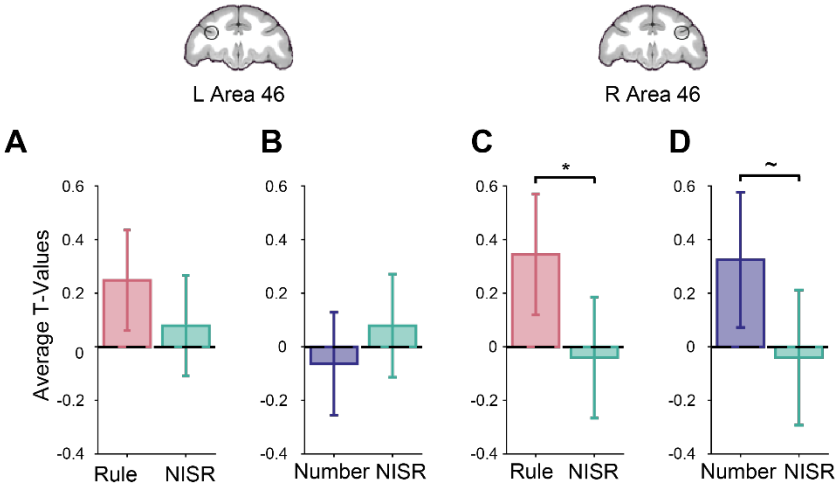


Figure 2. Area 46 represents abstract visual sequences. T-values for the condition of interest > baseline are shown. The locations of area 46 regions of interest (ROIs), L46 and R46, are outlined in black on coronal sections (y = 33). **A.** Rule deviants compared to new items, same rule (NISR) in L46. **B.** Number deviants compared to NISR in L46. **C.** Rule deviants compared to NISR in R46 showed a reliable difference. **D.** Number deviants compared to NISR in R46 showed a marginal difference. Comparisons in L46 showed similar trends as in R46. Error bars are 95% confidence intervals (1.96 x standard error of the within-bin mean).

457 **Table 1**. Repeated measures ANOVAs comparing rule and number deviants to NISR in L46 and R46.

		L46			R 46		
Factor	***dfs***	**F**	**p**	η_p^2	**F**	**p**	η_p^2
Rule Deviants > NISR							
Sequence Type	1, 19	0.39	0.54	0.02	4.6	0.046	0.19
Monkey	2, 19	3.55	0.049	0.27	1.4	0.28	0.13
Monkey x Sequence Type	2, 19	1.15	0.34	0.11	2.9	0.078	0.24
Number Deviants > NISR							
Sequence Type	1, 19	0.51	0.48	0.03	3.9	0.062	0.17
Monkey	2, 19	3.8	0.041	0.29	0.76	0.48	0.074
Monkey x Sequence Type	2, 19	0.098	0.91	0.01	5.15	0.016	0.35
Habituation > NISR							
Sequence Type	1, 19	0.0053	0.94	0.0003	1.6233	0.33	0. 051
Monkey	2, 19	4.35	0.028	0.31	3.37	0.48	0.26
Monkey x Sequence Type	2, 19	0.45	0.64	0.05	1.6	0.22	0.15

458

459

460 **Table 2**. Repeated measures ANOVAs comparing deviant responses in L46 and R46.

		Rule Deviants > NISR			Number Deviants > NISR		
Factor	***dfs***	**F**	**p**	η_p^2	**F**	**p**	η_p^2
R46 > L46							
Sequence Type	1, 40	3.6	0.07	0.08	0.85	0.36	0.02
Monkey	2, 40	4.15	0.02	0.17	1.14	0.33	0.05
Brain Area	1,40	0.005	0.94	0.0001	0.67	0.42	0.016
Monkey x Sequence Type	2, 40	0.54	0.6	0.026	2.88	0.07	0.13
Brain Area x Sequence Type	1,40	0.51	0.48	0.012	2.7	0.11	0.06

461

462 As a control, we also examined conditions where the pool of images differed, but the abstract
463 sequential structure did not. If area 46 was responding specifically to a change in the abstract
464 sequential structure, then a change in the images should not change its activation level. We
465 examined the difference in contrast t-values between NISR and habituation trials with
466 comparable stimulus durations ("medium" timing, as in **Figure 1D**). We did not find any

467 significant differences between these conditions in either R46 or L46 (**Table 1**), indicating that
468 changes in activation in area 46 were specific to changes in abstract sequential structure.

469 Results from area 46 ROIs were supported by whole-brain contrasts examining responses to
470 number and rule deviants. Contrasts of Rule Deviants > NISR and Number Deviants > NISR
471 both showed significant clusters of activation in right area 46 (**Figure 3**, **Table 3**, **Extended**
472 **Data Figure 3-1**). Other significant clusters of activation were located in areas such as the
473 caudate nucleus, high-level auditory cortex (rostromedial belt region), and dorsal premotor
474 cortex, areas also observed in a similar auditory sequence task (Wang et al., 2015). Further,
475 deviant responses in earlier sensory areas (e.g., V2) may be analogous to responses in auditory
476 cortex previously observed. Though we could not address the question of sensory generality
477 within the current experiment, these results raise the intriguing possibility that these previously
478 indicated areas could be sensory-modality general in their responses to abstract sequential
479 structure.

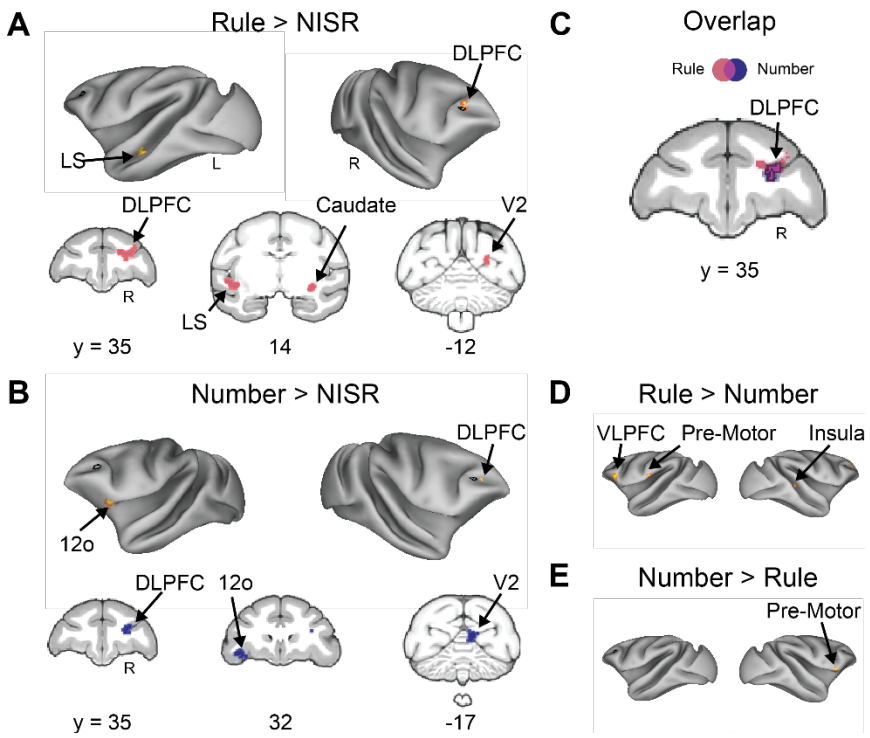


Figure 3. Whole-brain deviant activity shows area 46 represents both rule and number deviants. A. Voxel wise contrast of Rule Deviants > NISR false discovery rate (FDR) error cluster corrected for multiple comparisons (FDRc < 0.05, height p < 0.005 unc., extent = 130) are shown. Individual monkey data shown in **Extended Data Figure 3-1A**. **B.** Voxelwise contrast of Number Deviants > NISR (FDRc < 0.05, height p < 0.005 unc., extent = 132). Individual monkey data shown in **Extended Data Figure 3-1B**. **C.** Overlap of Rule Deviants > NISR and Number Deviants > NISR contrasts showed significant, unique conjunction (violet outlined in black) only in the DLPFC. **D.** Voxelwise contrast of Rule Deviants > Number Deviants showing no significant clusters of activation in area 46 (FDRc < 0.05, height p < 0.005 unc., extent = 102). **E.** As in (C) for Number Deviants > Rule Deviants (FDRc < 0.05, height p < 0.005 unc., extent = 111). Black outline on inflated brains indicates location of L46 or R46 (depending on the hemisphere shown) for reference. Lateral Sulcus (LS), Dorsal Lateral Pre-frontal Cortex (DLPFC), Ventral Lateral Pre-frontal Cortex (VLPFC), Secondary Visual Cortex (V2), Orbital Prefrontal Area (12o).

493 **Table 3**. Rule and number deviants compared to NISR contrast activation coordinates. Area labels as in the NIMH

494 NMT v02 Macaque Atlas.

Contrast Location	Extent (voxels)	x	y	z	Peak t-val
Rule Deviant > NISR					
Dorsolateral Prefrontal Cortex (46d)	282	10.5	34.5	21.5	4.24
		14	36	26	3.88
Medial Prefrontal Cortex (10mr)	195	0	47.5	17	5.96
Dorsal Pre-motor Cortex(6DR)		13	21	25	
Motor Cortex (F1)	213	-11	16.5	32	5.58
Caudate Nucleus (cd)	130	14.5	13	8	3.88
	138	-14.5	11.5	7.5	4.09
Lateral Sulcus/Auditory Cortex (RM)	282	-21	13.5	9	5.59
Secondary Visual Cortex (V2)	207	8.5	-15	21	4.34
Cerebellum					
Number Deviants > NISR					
Dorsolateral Prefrontal Cortex (Area 46d)	168	9	35	21.5	6.44
Orbital Prefrontal Area (12o)	162	-16	32	9.5	5.13
Secondary Visual Cortex (V2)	132	4.5	-16.5	18.5	4.96

495

496 To determine if the observed responses to number and rule deviants were similar in area 46, we

497 directly examined whether these responses generalized across deviant types. The t-values in R46

498 were not different between rule and number deviants (sequence type: $F(1,19) = 0.0011$, $p = 0.92$,

499 $\eta_p^2 = 0.11$, monkey: $F(2, 19) = 2.5$, $p = 0.11$, $\eta_p^2 = 0.21$; monkey x sequence type: $F(2, 19) =$

500 1.15, $p = 0.34$, $\eta_p^2 = 0.11$). Next, we performed a conjunction analysis to determine the areas of

501 activation that overlapped in the Rule Deviants > NISR and Number Deviants > NISR contrasts.

502 We found that the only cluster of significant overlap between the deviant contrasts was in right

503 area 46 (**Figure 3C**). In support of this finding, whole-brain direct contrasts of rule and number

504 deviants showed significant activation clusters in VLPFC, insula, and pre-motor cortex, but no

505 significant clusters in area 46 (**Figure 3D, E**). In summary, these results suggest that abstract

506 visual sequential structure is monitored in area 46, and that this monitoring is both unique to area
507 46 and general across different kinds of deviations.

508 **Ramping activation reflects sequence monitoring in monkey DLPFC**

509 We next tested the prediction that area 46 would display similar dynamics to those observed in
510 humans during abstract sequences. Specifically, previous experiments in humans showed that
511 BOLD activity increased ("ramped") from the beginning to the end of sequences in the RLPFC
512 (Desrochers et al., 2015, 2019; McKim and Desrochers, 2022). Given the similarity in
513 connectivity between monkey area 46 and human RLPFC, we hypothesized that changes in
514 abstract sequence structure would also produce changes in ramping activation in area 46 if
515 abstract sequence monitoring underlies this dynamic.

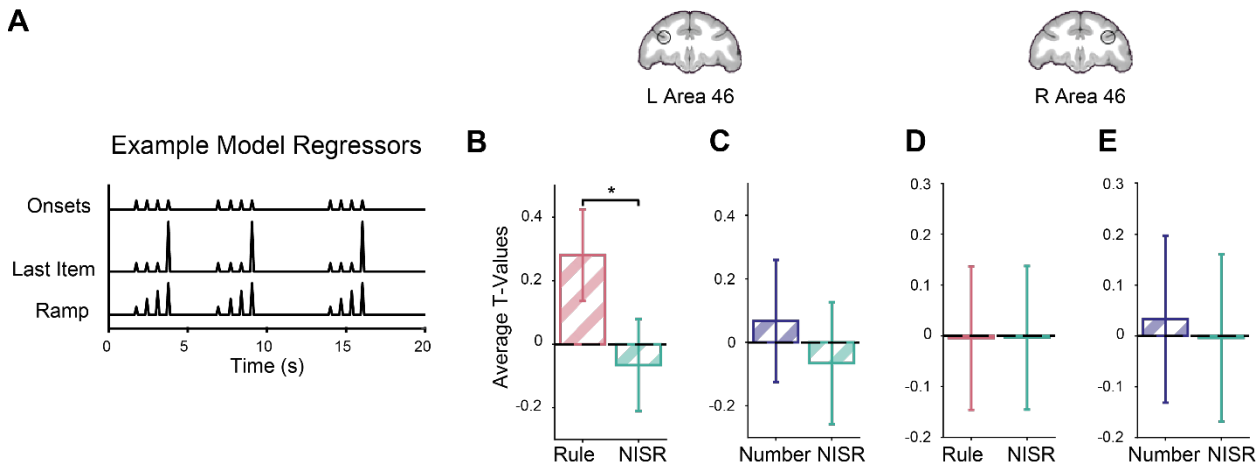
516 To test if ramping dynamics were present in area 46 during this task, we first designed a model
517 to isolate these dynamics. This model included regressors for the three dominant potential
518 dynamics (**Figure 4A**, **Extended Data Figure 4-1**, see also Materials and Methods). First,
519 instantaneous onsets were included for each image presentation, effectively modeling sustained
520 activation throughout each sequence. Then, two parametric regressors were included: last item
521 change and ramping. The ramping regressor parallels the analysis that revealed ramping in
522 human RLPFC: it increases linearly from the first to the last item in the sequence, and resets at
523 each new sequence. The last item change regressor is low at the first three positions of each
524 sequence, and high at the last item in the sequence. This regressor was designed to account for
525 the fact that differences in the rule that the sequence followed would occur at the last item (e.g.,
526 the difference between AAAA and AAAB occurs at the fourth item), and a dynamic associated
527 with this change could have variance mistakenly assigned to a ramping regressor.

These parametric regressors were orthogonalized in a stepwise fashion and only absorbed variance above and beyond variance accounted for by the onset regressor. The last regressor, therefore, contained "unique" variance. A pair of models, one with unique variance assigned to ramp and one with it assigned to last item, were created to examine these dynamics. The correlation between the resulting regressors was, as expected, low. For example, in one bin of this parametric model with the unique variance assigned to ramp, the average correlation coefficient between last item change and ramp regressors was 0.00005 (± 0.0001 standard deviation). While there are likely nearly infinite variations of dynamics possible that lie across a spectrum between the last item change and ramping (e.g., exponential), our purpose in designing these models was not to explore the space of all possible dynamics, but to test for ramping dynamics in area 46.

We found ramping dynamics in monkey area 46 related to abstract sequence monitoring. When comparing t-values of contrasts between deviants and baseline using the same spherical area 46 ROIs described above, we observed significant, unique variance ascribed to ramping activation in L46 during rule deviants compared to NISR (sequence type: $F(1, 19) = 5.03$, $p = 0.037$, $\eta_p^2 = 0.21$; **Table 4**; **Figure 4B**). Unique ramping activation showed a numerical trend in the same direction for number deviants compared to NISR in L46, but it did not reach statistical significance (**Table 4**). Activity in L46 was not reliably different between the two deviant types (sequence type: $F(1,19) = 2.06$, $p = 0.17$, $\eta_p^2 = 0.098$, monkey: $F(2, 19) = 0.57$, $p = 0.64$, $\eta_p^2 = 0.06$; monkey x sequence type: $F(2, 19) = 2.01$, $p = 0.16$, $\eta_p^2 = 0.17$). In R46, changes in unique ramping activation during rule and number deviants were not significant (**Table 4**). Despite apparent differences between L46 and R46, unique ramping was not reliably different between these ROIs (**Table 5**). These results suggest that area 46 shows ramping dynamics for sequential

551 rule changes. Interestingly, ramping may be preferentially present in L46, suggesting that while
552 both hemispheres detect abstract sequence deviations, they may do so with different dynamics.
553 Further, these results suggest similar sequential monitoring processes may be present across
554 species in analogous areas.

555



556

557 **Figure 4. Area 46 shows ramping activity for deviations to an established sequence rule.** Parametric models and
558 T-values for the condition of interest > baseline shown. Coronal brain slices (y = 33) show locations of area 46
559 ROIs, L46 and R46, outlined in black. **A.** Example of regressors used to model parametric ramp and parametric last
560 item. Example regressors through the orthogonalization process shown in **Extended Data Figure 4-1**. **B.** Unique
561 ramping during rule deviants compared to NISR in L46 showed a reliable difference. **C.** Unique ramping during
562 number deviants compared to NISR in L46. **D.** Unique ramp number deviants compared to NISR in R46. **E.** Unique
563 ramping during number deviants compared to NISR in R46. Comparisons that were not reliably different showed
564 similar trends. Error bars are 95% confidence intervals (1.96 x standard error of the within-bin mean).

565 **Table 4**. Repeated measures ANOVAs comparing unique ramping activity during rule and number deviants to NISR
566 in L46 and R46.

		L46			R 46		
Factor	***dfs***	**F**	**p**	**η_p^2**	**F**	**p**	**η_p^2**

Unique Ramp, Rule Deviants > NISR							
Sequence Type	1, 19	5.03	0.037	0.21	0.01	0.91	0.00075
Monkey	2, 19	0.82	0.45	0.08	0.64	0.54	0.63
Monkey x Sequence Type	2, 19	0.23	0.8	0.0235	0.81	0.46	0.08
Unique Ramp, Number Deviants > NISR							
Sequence Type	1, 19	0.42	0.52	0.02	0.03	0.86	0.0016
Monkey	2, 19	2.39	0.12	0.2	0.24	0.45	0.08
Monkey x Sequence Type	2, 19	5.15	0.63	0.047	5.15	0.84	0.0235

Table 5. Repeated measures ANOVAs comparing unique ramping deviant responses in L46 and R46.

		Unique Ramp, Rule Deviants > NISR			**Unique Ramp, Number Deviants > NISR**		
Factor	***dfs***	**F**	**p**	η_p^2	**F**	**p**	η_p^2
R46 > L46							
Sequence Type	1, 40	0.38	0.54	0.009	2.4	0.13	0.06
Monkey	2, 40	1.62	0.21	0.07	1.5	0.24	0.07
Brain Area	1, 40	0.02	0.89	0.0005	1.5	0.25	0.03
Monkey x Sequence Type	2, 40	0.64	0.53	0.03	0.12	0.89	0.006
Brain Area x Sequence Type	1, 40	0.14	0.71	0.003	2.7	0.11	0.06

Because variance due to changes at the last item of the sequence could be misattributed to ramping regressors, we directly compared activity in area 46 that could be accounted for by ramping and last item change regressors. In this control analysis, we found that activity was significantly greater for unique ramping than unique last item change during rule deviants in L46 (sequence type: $F(1, 19) = 9.53$, $p = 0.006$, $\eta_p^2 = 0.33$; **Table 6**; **Figure 5A**). Number deviants in L46 and both deviants in R46 showed similar numerical trends for unique ramping accounting for greater variance than last item change but did not reach statistical significance (**Figure 5B-D**; **Table 6**). These results suggest that area 46 dynamics during abstract sequence monitoring are best accounted for by a ramping function, rather than a last item change.

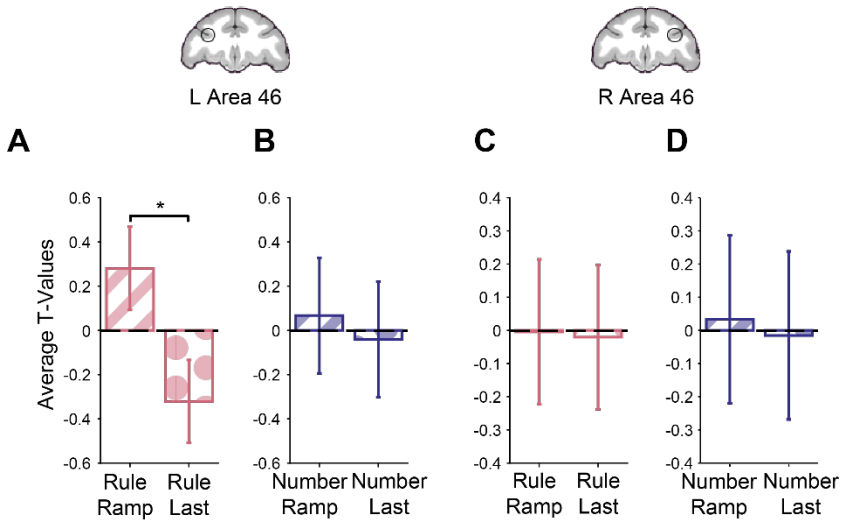


Figure 5. Area 46 shows greater unique ramping than unique last item activity during abstract sequence deviants. T-values for the condition of interest > baseline shown. **A.** Unique ramp compared to unique last item during rule deviants in L46 showed a reliable difference. **B.** Unique ramp compared to unique last item during number deviants in L46. **C.** Unique ramp compared to unique last item during rule deviants in R46. **D.** Unique ramp compared to unique last item during number deviants in R46. Comparisons that were not reliably different showed similar trends. Error bars are 95% confidence intervals (1.96 x standard error of the within-bin mean).

Table 6. Repeated measures ANOVAs comparing unique ramping activity to unique last item activity during rule and number deviants to NISR in L46 and R46.

		L46			**R 46**		
Factor	***dfs***	**F**	**p**	η_p^2	**F**	**p**	η_p^2
Unique Ramp, Rule Deviants > Unique Last Item, Rule Deviants							
Sequence Type	1, 19	9.53	0.006	0.33	0.008	0.93	0.0004
Monkey	2, 19	1.02	0.38	0.97	0.72	0.5	0.07
Monkey x Sequence Type	2, 19	0.37	0.7	0.38	0.09	0.91	0.01
Unique Ramp, Number Deviants > Unique Last Item, Number Deviants							
Sequence Type	1, 19	0.196	0.66	0.01	0.07	0.8	0.0036
Monkey	2, 19	2.08	0.15	0.18	1.47	0.25	0.13
Monkey x Sequence Type	2, 19	1.26	0.31	0.12	0.15	0.86	0.015

591 ROI results were supported by whole-brain contrasts that examined ramping and last item
592 dynamics. Unique ramping was present in left area 46 during rule deviants compared to NISR
593 (**Figure 6A, Table 7, Extended Data Figure 3-1C**). Other clusters of activation were present in
594 the visual cortex and superior temporal gyrus that were similar to those observed for ramping
595 activation in humans (Desrochers et al., 2015, 2019). As expected from the ROI analyses, the
596 number deviant ramping contrast had significant whole brain clusters in areas such as visual
597 cortex and putamen but no significant clusters in area 46 (**Figure 6B, Table 7**). The localization
598 of significant unique last item clusters was different than ramping. Specifically, a more anterior
599 region of ventral area 46 (46v), in contrast to more posterior and dorsal area 46 (46d) observed
600 for unique ramping, showed significant activation for unique last item change in rule deviants
601 compared to NISR (**Figure 7A, Table 8**). Other significant clusters of activation for last item
602 change included the somatosensory cortex and central orbitofrontal cortex (area 13m). We also
603 contrasted unique last item variance in number deviants compared to NISR, and observed
604 activation in areas such as anterior cingulate gyrus, insula and visual cortices but no surviving
605 clusters in area 46 (**Figure 7B, Table 8**). These results suggest that subregions of area 46 within
606 the same hemisphere may reflect separable aspects of changes in sequential structure.

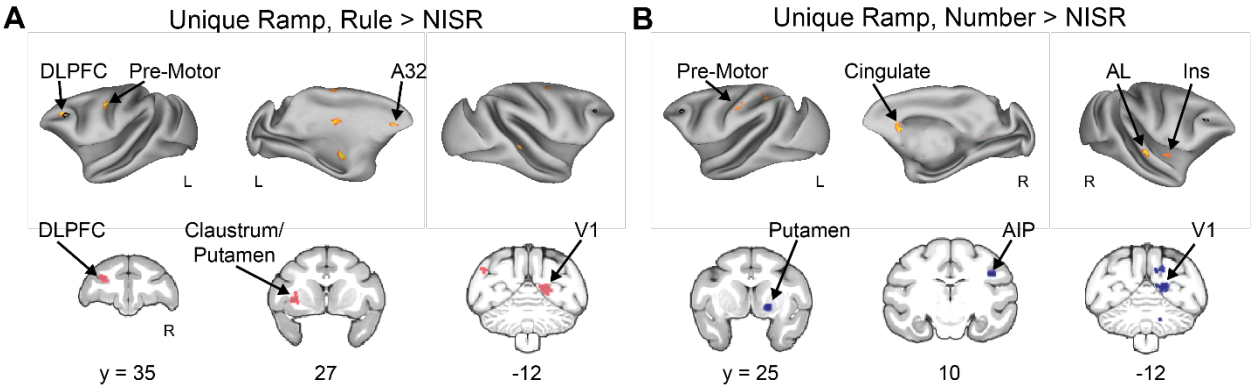


Figure 6. Area 46 shows unique ramping during abstract sequence deviants. A. Unique Ramp, Rule Deviants > NISR (FDRc $p < 0.05$, height $p < 0.005$ unc., ext. 82). Individual monkey data shown in **Extended Data Figure 3-1C**. **B.** Unique Ramp, Number Deviants > NISR (FDRc $p < 0.05$, height $p < 0.005$ unc., ext. 89). Black outline on inflated brains indicates location of L46 or R46 (depending on the hemisphere shown) for reference. Medial Prefrontal Cortex (A32) Dorsal Lateral Pre-frontal Cortex (DLPFC), Primary Visual Cortex (V1), Insular Cortex (Ins), Anterior Lateral Belt Region of the Auditory Cortex (AL), Anterior Intraparietal Area (AIP).

Table 7. Unique ramp rule and number deviants compared to NISR contrast activation coordinates.

Contrast Location	Extent (voxels)	x	y	z	Peak t-val
Unique Ramp, Rule Deviants > NISR					
Primary Motor Cortex (F1)	153	11	13.5	29.5	6.48
Caudal Dorsal Pre-Motor Cortex (PMdc)	89	12	18	34.5	6.17
Dorsal Dorsal Lateral Prefrontal Cortex (46d)	130	-12.5	36	23	5.34
Intraparietal Area (IPa)	121	16	18.5	2	5.33
Rostral Area 12 (12r)	128	-15	29	14.5	5.19
Caudate Nucleus (Cd)	385	-10.5	19	23	5.15
Caudal Pre-Motor Cortex (PMdc)	113	-18.5	20	30	5
Secondary Visual Cortex (V2)	82	28	-7.5	14.5	4.67
Primary Visual Cortex (V1)	101	-20.5	-11	27	4.66
Body of the Fornix (bfx)	120	-1.5	12.5	22.5	4.49

Somatosensory Parietal Cortex (1,2)	120	-13	7.5	33.5	4.4
Primary Motor Cortex (M1)	97	-3.5	14.5	38	4.3
Medial Septum (ms)	82	-1	18.5	13	4.18
Secondary/Primary Visual Cortex (V2/V1)	129	9	-11	19	4.16
Intraparietal Area (IPa)	97	18.5	7.5	16	4.01
Globus Pallidus (MGPi)	250	-6.5	13	8	3.99
Pre-genual Cortex (24a)	101	-2	38.5	17	3.96
Unique Ramp, Number Deviants > NISR					
Visual Area 3 (V3)	163	7.5	-12.5	26.5	6.42
Anterior Lateral Belt Region (AL)	130	28	17	12.5	6.35
Agranular and Dysgranular Insula (Ia/Id)	103	21	19	10.5	5.62
Putamen (Pu)	127	7	24.5	10.5	5.5
Caudate Nucleus (Cd)	772	-5.5	20	18	5.29
Primary Visual Cortex (V1)	132	9	-11.5	19	5.16
Cerebellum	250	7	-15.5	12	4.85
Somatosensory Parietal Cortex (1,2)	89	-4.5	4	35	4.72
Cerebellum	138	4	-18	5.5	4.67
Anterior Intraparietal Area (AIP)	123	18.5	10.5	25.5	4.65
Somatosensory Parietal Cortex (1,2)	115	-21	13	32.5	4.5
Caudal Dorsal Pre-Motor Cortex (PMdc)	324	-10.5	20	28	4.45
Ventral Tegmental Area (VTA)	282	-4	4	3	4.37
Posterior Cingulate Gyrus (23c)	100	-7.5	5.5	30.5	4.07
Somatosensory Parietal Cortex (1,2)	152	-12.5	6.5	35	4.01

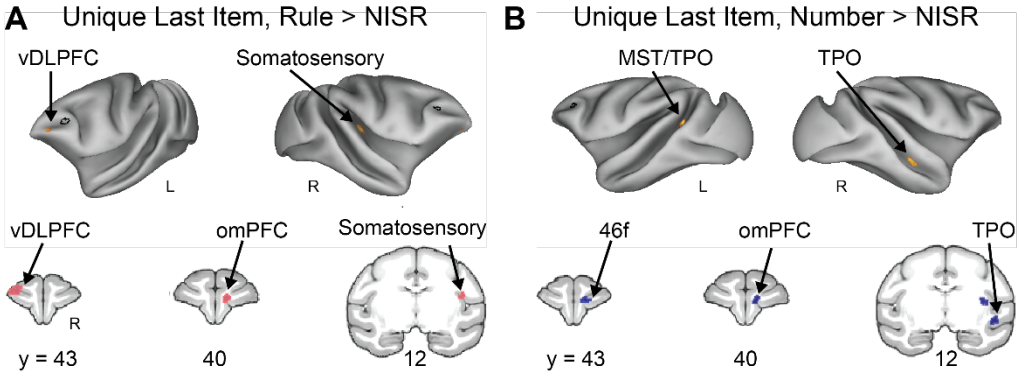


Figure 7. DLPFC does not show significant responses to unique last items during abstract sequence deviants. **A.** Unique Last Item, Rule Deviants > NISR (FDRc < 0.05, height p < 0.005 unc., extent = 148). **B.** Unique Last Item, Number Deviants > NISR (FDRc < 0.05, height p < 0.005 unc., extent = 82). Black outline on inflated brains

622 indicates location of L46 or R46 (depending on the hemisphere shown) for reference. Ventral Dorsal Lateral
623 Prefrontal Cortex (vDLPFC), Medial Superior Temporal Cortex (MST), Superior Temporal Sulcus Dorsal Bank
624 (TPO), Orbital Medial Prefrontal Cortex, Fundus of the Dorsal Lateral Prefrontal Cortex (46f).

625

626 **Table 8**. Unique last item rule and number deviants compared to NISR contrast activation coordinates.

Contrast Location	Extent (voxels)	x	y	z	Peak t-val
Unique Last Item, Rule Deviants > NISR					
Ventral Dorsal Lateral Prefrontal Cortex (46v)	148	-12	43	22	5.23
Granular Insula (Ig)	170	19	11	20	5.06
Medial Area 11 (11m)	156	3.5	41	17.5	4.93
Ventral Intraparietal Area/White Matter (VIP/WM)	360	8.5	-1	22.5	4.1
Unique Last Item, Number Deviants > NISR					
Area TFO (TFO)	121	-14	4	1.5	5.75
Caudate Nucleus	82	1	29.5	16.5	5.32
Primary Visual Cortex (V1)	247	-8.5	-18.5	12	5.13
Area 13 (13m)	184	4	38	18.5	4.92
Cerebellum	90	12.5	-12.5	5	4.89
Granular Insula (Ig)	117	17.5	16	15.5	4.36
Temporal Parietooccipital Associated Area (TPO)	88	21.5	14	7.5	4.32
Caudomedial Belt Region (CM)	116	-15	2.5	22	4.19
Anterior Cingulate Gyrus (24a)	85	-2	28.5	20.5	4.14
Posterior Cingulate Gyrus (29)	151	7	0.5	20.5	4.03

627

628 To determine if clusters of activation for unique ramping and unique last item were separable in
629 the frontal cortex, we directly compared the amount of variance assigned to each cluster for both
630 dynamics. One possibility is that, due to thresholding at the whole-brain level, there was similar

activation for each dynamic across areas 46d and 46v, but that the peak, and thus the location of the thresholded cluster, differed slightly in location. To address this possibility, we created two ROIs from the clusters of significant activation in Unique Ramp, Rule Deviants > NISR contrast (area 46d, center *xyz* = -12.2, 36, 23.8 mm), and Unique Last Item, Rule Deviants > NISR contrast (area 46v, center *xyz* = -12.3, 42.9, 21.8 mm). We found a significant interaction between ROI and model in rule deviants compared to NISR (**Figure 8**; sequence type: $F(1, 40) = 0.13$, $p = 0.71$, $\eta_p^2 = 0.003$; monkey: $F(2, 40) = 2.23$, $p = 0.12$, $\eta_p^2 = 0.1$; brain area: $F(1, 40) = 0.09$, $p = 0.77$, $\eta_p^2 = 0.002$; monkey x sequence type: $F(2, 40) = 0.33$, $p = 0.72$, $\eta_p^2 = 0.016$; brain area x sequence type: $F(1, 40) = 29.3$, $p < 0.001$, $\eta p2 = 0.42$), indicating that responses in the ramping and last item clusters were reliably different. As expected from the whole-brain contrasts, there was no significant interaction for number deviants compared to NISR (not shown; $F(1, 40) = 0.796$, $p = 0.38$, $\eta_p^2 = 0.02$). These results show that these nearby clusters in dorsal and ventral area 46 are separable in their dynamics.

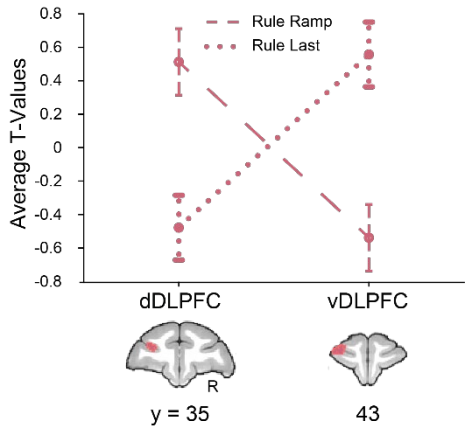


Figure 8. Nearby regions of DLPFC show significantly different dynamics. ROIs constructed from significant areas of activation in unique ramping (46d, dDLPFC) and unique last item (46v, vDLPFC) contrasts shown on

coronal sections. T-values for the condition of interest > baseline shown. Models show a double dissociation in left area 46 during rule deviants. Error bars are 95% confidence intervals (1.96 x standard error of the within-bin mean).

Discussion

In this study, we examined if and how monkey DLPFC (area 46) monitors abstract sequential information. We tested two main hypotheses: First, that evidence of abstract sequence monitoring would occur in the area of monkey DLPFC analogous to human RLPFC previously shown to be critical for abstract sequential tasks (Desrochers et al., 2015, 2019; McKim and Desrochers, 2022); and, second, that ramping dynamics would be associated with abstract sequence monitoring and show changes when abstract sequential structure changed. These hypotheses were tested in a no-report sequence viewing task that allowed the isolation of dynamics associated with sequence monitoring from other potential confounds such as motor preparation. We found evidence to support both hypotheses. Right area 46 responded to abstract sequence changes in both rule and number. Interestingly, left area 46 also responded to changes in abstract sequential rules, but with ramping dynamics that were similar to those observed in humans and separable from an increase only at the last item. These results suggest that a specific subregion of monkey DLPFC is specialized for monitoring general visual abstract sequential information and is a point of critical potential functional homology between human and monkey PFC during higher-level cognitive function.

The activation patterns found, with ramping dynamics primarily on the left and onset-based on the right, are consistent with prior findings. Though not explicitly tested, in humans ramping was observed preferentially on the left during abstract sequential tasks (Desrochers et al., 2015, 2019), Experiment 1) in contrast to bilateral ramping activation observed in tasks where

670 sequences were based on stimulus identity (i.e., ordered visual items; (Desrochers et al., 2019),
671 Experiment 2; (McKim and Desrochers, 2022). These human results are also consistent with the
672 long-standing literature that emphasizes abstract cognitive functions in the left hemisphere of
673 humans (e.g., (Badre and D'Esposito, 2007; Bunge et al., 2009; Wendelken et al., 2012), with the
674 most famous such example being language (Broca, 1861; Milner, 1971; Petrides, 2013).
675 Ramping activity has been observed in human frontal cortex during sequential language
676 information processing (i.e., sentence comprehension) with electrocorticography (ECoG)
677 (Fedorenko et al., 2016). While generally consistent with prior work, future studies of the distinct
678 left and right hemisphere activation dynamics will be needed to determine their underlying
679 drivers and their potential cognitive import. In particular, the present findings suggest that neural
680 dynamics underlying DLPFC sequence monitoring may be distinct to each hemisphere. The
681 monkey fMRI findings described here can provide a guide for such recordings. In sum, our
682 results raise the possibility that the representation in and contribution of DLPFC to abstract
683 sequence monitoring is lateralized in monkeys, and provide a road map to future studies.

684 An advantage of fMRI is the whole brain view that is not afforded by typical
685 electrophysiological techniques in macaques. This view leads to potential insights about
686 functional organization of brain areas without the limitations of a recording chamber (Milham et
687 al., 2022). For example, in recent literature, fMRI has enabled the mapping of projections to and
688 from the PFC with a level of specificity and across distances not previously possible on this scale
689 (Xu et al., 2022). This work found an overlap in topographically organized high-level visual
690 maps from the dorsal and ventral streams in primate lateral prefrontal cortex. These results raise
691 the possibility that the localization of abstract visual sequence monitoring in DLPFC results from
692 its position near the apex of highly organized visuo-spatial maps. The overarching organization

693 of more cognitive processes in monkey frontal cortex has remained more elusive (Hutchison and
694 Everling, 2014; Neubert et al., 2014, 2014; Saleem et al., 2014), and the results presented here
695 represent a critical step forward in understanding their topography.

696 We observed similarities and differences to a previous study using a similar auditory task (Wang
697 et al., 2015) that may reflect the modality employed and the capacity for generalization. Areas of
698 the brain that responded to deviant sequences in both the current visual and prior auditory studies
699 may be modality general. These areas included premotor cortex, caudate nucleus, and the
700 auditory cortex rostromedial belt. In contrast, brain areas that uniquely responded to deviants in
701 the auditory or this visual task may be modality specific for abstract sequence changes. For
702 example, deviant responses in ventral LPFC and superior temporal sulcus were unique to the
703 auditory study. In this visual task, deviant responses in DLPFC, visual cortex, and mPFC were
704 observed that were not observed in the auditory task. Though we cannot draw strong conclusions
705 without direct comparison between the modalities, these results suggest that networks of brain
706 areas that partially overlap may constitute abstract sequence tracking across modalities. One
707 further important difference in the studies is that in the auditory study, there was a lack of
708 overlap between areas that respond to rule and number deviants in the monkey (in contrast to the
709 human). Here, we observed overlap in these responses in area 46, suggesting a higher level of
710 visual integration in the monkey. The question of sensory domain generality and integration
711 remains open to further investigation.

712 The results observed here in this no-report abstract sequence viewing task in monkeys are similar
713 to those observed in humans during sequential tasks in important ways. First, ramping activation
714 was observed in similar regions in the frontal cortex in the monkey (area 46) and human

715 (RLPFC). Other similar areas included visual cortex, putamen, and pre-motor cortex (Desrochers
716 et al., 2015, 2019; McKim and Desrochers, 2022). Though the current experiment was only
717 designed to detect the presence of ramping in relation to abstract sequences, by analogy, the
718 function may be similar in the lateral prefrontal cortex across species. Ramping activity has been
719 ascribed to many possible functions across species, including accumulating evidence (de Lange
720 et al., 2010; Krueger et al., 2017; Darriba and Waszak, 2018; Lin et al., 2020), keeping time
721 (Nobre et al., 2007; Berdyyeva and Olson, 2011; Cueva et al., 2020), reward anticipation
722 (Roesch and Olson, 2007; Horst and Laubach, 2013; Chiew et al., 2016; Falcone et al., 2019;
723 McKim and Desrochers, 2022) and monitoring sequence position (Desrochers et al., 2015,
724 2019). These possibilities are not mutually exclusive, as recent evidence in humans suggests that
725 reward anticipation and sequence information may be present simultaneously in this signal
726 (McKim and Desrochers, 2022). The current experiment identified ramping in the DLPFC as
727 being sequence related, but did not examine other potential influences and therefore remains an
728 open avenue of future inquiry. Similarly, other brain areas that display ramping activation remain
729 open for investigation.

730 Though this study bears resemblance to a field of literature using statistical learning paradigms,
731 the majority of those studies use tasks that rely on the identity of the stimuli themselves.
732 Importantly, this study is distinct from most statistical learning studies because the identity of the
733 stimulus alone cannot predict the following item (i.e., knowing the current fractal is the green
734 one does not determine the next stimulus without also having sequential rule information). A
735 subset of work in the infant learning literature examines statistical learning that is not dependent
736 on stimulus identity (i.e., “artificial grammar”), but mostly auditory tasks were used (e.g.,
737 (Saffran et al., 1996)). To our knowledge, only one behavioral study examined violations to a

visual (and auditory) artificial grammar where sequences of different lengths are constructed according to set transition probabilities (Milne et al., 2018). While the findings were important because violations were detected similarly in monkeys and humans, there were no neural data presented. Further, while transition probabilities created the sequences, there was not a set "rule" by which they were constructed. Therefore, the present study is unique in examining neural responses to abstract visual sequences.

This study contained the following limitations. First, the timing of the stimuli in the current design did not allow examination of dynamics of individual sequence items, only across the sequence as a whole. In a single experiment, it was not feasible to separate each sequential item by the time required to model each separately in an event-related design. Therefore, future work will aim to examine the dynamics of individual sequential items in greater detail. Second, while the no-report task allowed the elimination of motor preparatory confounds, it did not allow for direct correlation with behavioral performance. Although the observed signals will potentially also underlie tasks that require responses, this assertion remains to be tested and the present study is an important foundation for further experiments. Third, we have focused here on the DLPFC because although its importance in cognitive processes in monkeys has been established, its response to visual abstract sequences and potential correspondence to dynamics in humans remained unknown. The DLPFC is part of a network of areas active in this task, and although they are outside the scope of the current experiment, they remain an important avenue of future research.

In summary, we provide evidence that a specific subregion of monkey DLPFC monitors abstract visual sequences and generalizes across different sequence violations (number and rule). Further,

760 sequence related ramping dynamics were also observed in DLPFC. Importantly, this region is
761 possibly analogous to human RLPFC, where necessary sequence-related ramping signals have
762 been identified in the past. These results suggest functional homology across the species as to
763 where and how more general abstract visual sequential information is represented in the brain.
764 These findings, in turn, inform future models of how abstract sequential information is
765 represented during more complex behaviors across species.

766

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Extended Data

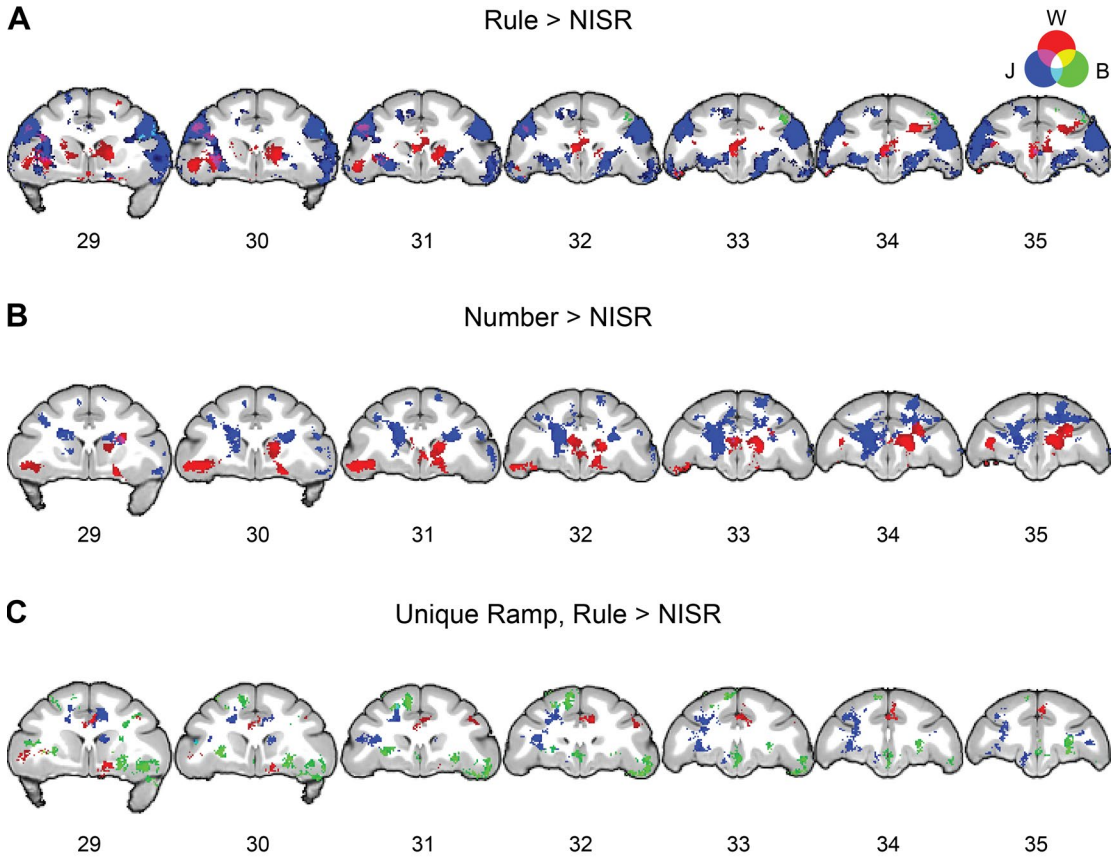

Figure 3-1. Overlaid individual monkey contrasts for monkeys W, J, and B. Three second level contrasts, one for each monkey, were created using only data bins that contained runs from each animal (W = 9, J = 6, B = 7 bins each). As described in Materials and Methods, each bin contained approximately 10 runs. A liberal height threshold of $p < 0.05$ was chosen for illustrative purposes before applying and extent (extents listed for each monkey by contrast) and false discovery rate (FDR) error cluster corrected for multiple comparisons to $p < 0.05$. Slice number in the y direction is listed under each coronal section. **A.** Voxel wise contrast of Rule Deviants > New Items, Same Rule (NISR) (W extent = 560, J = 1296, B = 623 voxels). **B.** Voxel wise contrast of Number Deviants > NISR (W

extent = 772, J = 750, B = 667 voxels). **C.** Voxel wise contrast of Unique Ramp, Rule Deviants > NISR (W extent = 560, J = 630, B = 581 voxels).

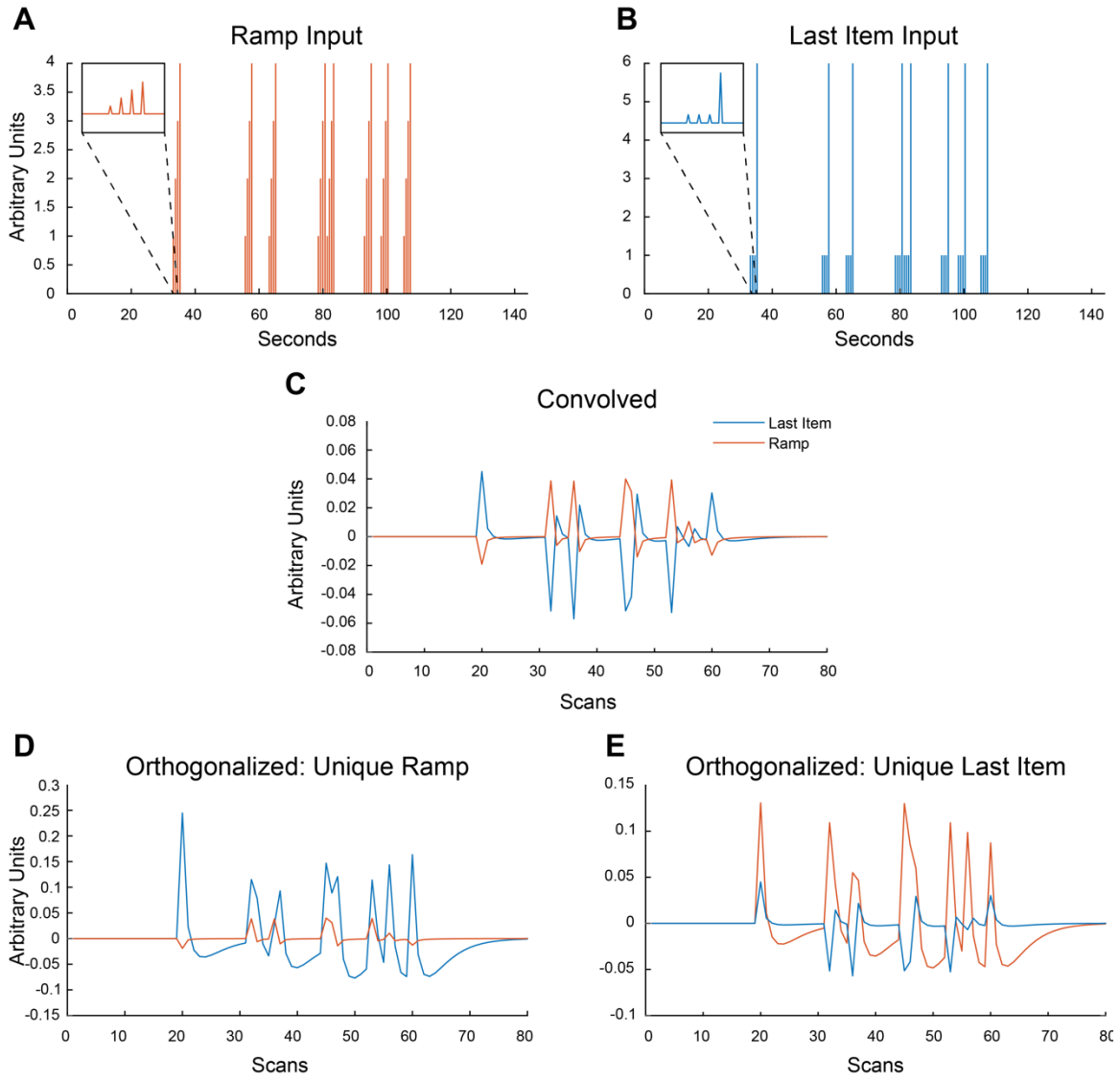

Figure 4-1. Example Ramp and Last Item regressors through the orthogonalization process. Note that SPM first creates regressors from onsets (in seconds, shown in **A.**) in samples using higher resolution to be convolved, and then they are down-sampled before being orthogonalized and entered in the GLM.