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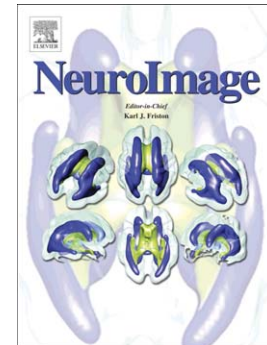
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Predictability of what or where reduces brain activity, but a bottleneck occurs when both are predictable

Abbreviated title: The impact of location and category regularities

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Abstract

Detecting regularities in the sensory environment licenses predictions that enable adaptive behaviour. However, it is unclear whether predictions about object category, location, or both dimensions are mediated by overlapping systems, and relatedly, whether constructing predictions about both category and location is associated with processing bottlenecks. To examine this issue, in an fMRI study, we presented participants with image-series in which non-deterministic transition probabilities enabled predictions about either the location of the next image, its semantic category, both dimensions, or neither (the latter forming a “no-regularity” random baseline condition). Speaking to a common system, all three predictable conditions resulted in reduced BOLD activity in four clusters: left rostral anterior cingulate cortex; bilateral putamen, caudate and thalamus; right precentral gyrus, and left visual cortex. Pointing to a processing bottleneck, in some regions, a significant interaction between the two factors was found whereby category-predictable series were associated with lower activity – but only when location regularity was absent. Finally, category regularity decreased activation in areas of the ventral visual stream and semantic areas of lateral temporal cortex, and location regularity decreased activation in a dorsal fronto-parietal cluster, long implicated in the endogenous control of spatial attention. Our findings confirm and expand a role for dACC/dmPFC and striatum in monitoring or responding to uncertainty in the environment and point to a limited capacity bottleneck when multiple predictions are concurrently licensed.

Keywords: uncertainty, prediction, statistical learning, predictive coding, disorder, entropy

1. Introduction

Humans excel at detecting regularities. They can detect patterns matching chaotic (non-random) processes, differentiate fractal dynamics across multiple time scales, and recognize subtle interactions between multiple variables (Lewicki, Hill, & Czyzewska, 1992; Smithson, 1997; Stephen & Dixon, 2011). This ability develops early (e.g., Saffran, Aslin, & Newport, 1996) and applies to both visual and non-visual input (for review, see Conway, Pisoni, & Kronenberger, 2009). Moreover, the ability to recognize temporally unfolding regularities or patterns in the sensory environment offers multiple advantages: it allows prediction when regularities exist, or conversely, an increased emphasis on bottom-up processing when the environment lacks regularity.

Much of the neurobiological research to date has focused on brain regions whose activity tracks regularity of simple visual or auditory streams. This work has linked several brain regions to the processing of regularity, including lateral and dorso-medial prefrontal cortex (dmPFC; Behrens, Woolrich, Walton, & Rushworth, 2007; Huettel, Song, & McCarthy, 2005), hippocampus (Bornstein & Daw, 2012; Harrison, Duggins, & Friston, 2006; Strange, Duggins, Penny, Dolan, & Friston, 2005), posterior parietal sulcus (Huettel et al., 2005; Nastase, Iacovella, & Hasson, 2014), anterior cingulate cortex (ACC; Harrison, Bestmann, Rosa, Penny, & Green, 2011; Nastase, Iacovella, Davis, & Hasson, 2015) and lateral temporal regions (e.g., Bischoff-Grethe, Proper, Mao, Daniels, & Berns, 2000; Tobia, Iacovella, & Hasson, 2012; Tremblay, Baroni, & Hasson, 2013).

While the use of simple tonal or visual series has proved effective for identifying mechanisms by which regularities are coded or deployed for purposes of prediction, these paradigms have not examined an important use of environmental regularities: making predictions about semantic features and location of elements in the environment that have yet to appear. In particular, it is unclear whether contexts that allow for joint predictions about the *location and identity* of future stimuli involve those neural systems engaged when only location or identity are predictable. It is also unclear whether the ability to predict both dimensions is associated with a processing bottleneck. As we review in detail below, there are two views on this issue. One view posits that separate systems code for different dimensions of the environment (location, visual features, etc'; see Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003), and these systems operate in parallel to encode location and category information (what appears where). In the other, a single core fronto-parietal system mediates anticipation of future locations and identity (Egner et al., 2008)

To address these issues, we conducted an fMRI study in which participants observed series of images that were drawn from four semantic categories and presented at four screen locations. The four types of series were constructed so that the transition structure allowed for predictions about *i)* just the location of the next image, *ii)* just its category, *iii)* both dimensions (dual regularity), or *iv)* neither dimension (the latter forming the “no-regularity” baseline condition). We examined activity in the baseline no-regularity condition vis-à-vis activity in the other three conditions, where predictions regarding location, category, or both were licensed. This allowed for identification of neural systems sensitive to statistical regularities in these domains and second, identification of systems where the ability to predict both location and category produced activation patterns consistent with a processing bottleneck.

From the perspective of experimental design, a bottleneck in predictive processing would appear as an interaction between the levels of location and categorical predictability. If the two dimensions were tracked by independent systems, those would show main effects of regularity in the categorical and location domains. However, if the two systems are integrated or interact each other, then the level of location regularity should affect the expression of categorical predictability or vice-versa. This interaction may be expressed in different forms and we were particularly interested to see if there would be brain areas where the dual regularity condition was associated with higher activity than both the location- and category-regularity conditions.

Our work assumes that environmental statistics are vital information for systems that mediate predictive coding – a computation in which systems associated with higher level functions generate predictions about expected environmental states – that is, construct a model of expected neural activity in low-level sensory regions (Friston, 2009; Grossberg, 2009; Rao & Ballard, 1999; Summerfield & Egner, 2009). Satisfied – i.e., correct -- predictions are associated with reduced prediction errors, and lower activity in sensory regions (Feldman & Friston, 2010; Kok, Rahnev, Jehee, Lau, & de Lange, 2012). Predictions may be instantiated and evaluated via interactions between frontal regions and sensory systems (Bar et al., 2006; Summerfield et al., 2006), or via interactions between sensory regions (den Ouden, Friston, Daw, McIntosh, & Stephan, 2009). A representation of stimulus regularity can license predictions about what is likely to appear where. This not only speeds up orientation towards, but also improves the identification of, a future stimulus via pre-sensitization of systems that code for its expectation. (e.g., Esterman & Yantis, 2010). The predictive coding framework makes well-defined hypotheses about the impact of statistically induced predictions regarding location and identity. However, as we detail below, it leaves open the *neurobiological question* of whether the potential to anticipate both location and category is associated, at any level, with increased difficulty as compared to conditions where only one of the dimensions is predictable.

With respect to location regularities, it has been shown that individuals are highly sensitive to them (Marcus, Karatekin, & Markiewicz, 2006; Walthew & Gilchrist, 2006). They respond faster to targets appearing in more predictable locations, either because these target locations have higher marginal frequencies (Geng & Behrmann, 2002, 2005; Jones & Kaschak, 2012) or because they are linked to stronger transition probabilities (Remillard, 2003, 2009). We therefore expected that being able to predict location transitions would serve as an endogenous cue, resulting in increased activity in regions associated with recruitment and directing of spatial attention, specifically the bilateral intraparietal sulcus and the frontal eye fields (see Corbetta & Shulman, 2002, and also Szczepanski & Kastner, 2013, for recent review). At the same time, the greater proportion of correct predictions should translate in reduced activity in visual cortex when location is predictable (~ V1; Kok et al., 2012).

In addition, we studied the impact of regularities governing the semantic categories from which visual images were drawn. This examination was more exploratory, since there is little if any prior work that informs this issue. Individuals are sensitive to the presence of fixed sequences of images drawn from basic-level categories (Brady & Oliva, 2008; Goschke & Bolte, 2012), but whether this extends to stochastic contexts has not been examined. As far as regions that might be sensitive to category in the

context of visual regularity, prior results point to lateral occipital cortex and the fusiform. These regions show stronger repetition-suppression effects when repetitions are more predictable, which has been taken to suggest they mediate anticipatory predictions (Mayrhauser, Bergmann, Crone, & Kronbichler, 2014; Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008). Importantly, reduced activity in these regions likely also reflects long-term familiarity with the stimuli (i.e., not solely a visual representation) as the pattern of repetition suppression in the fusiform depends on stimulus familiarity; Henson, Shallice, & Dolan, 2000). We thus hypothesized that being able to make category-level predictions would result in reduced activity across the lateral occipital cortex and fusiform. We note that our paradigm evaluated whether predictions could be made on the abstract level (of category, not specific tokens) as in our study all images were unique and presented once, making it impossible to predict the specific feature of the next image.

As mentioned above, some have argued that coding for multiple input streams relies on separate systems (e.g., Keele et al., 2003), whereas others have suggested that anticipating location and identity relies on a single system (e.g., Egner et al., 2008). Current approaches to statistical learning are similarly concerned about whether the capacity to learn the statistics of an input stream is mediated by a single, modality-general system, or carried out by additional more modality-specific systems (Frost, Armstrong, Siegelman, & Christiansen, 2015). Our own prior work on this matter, which manipulated regularities in auditory-only or visual-only streams, showed that separate systems might be involved (Nastase et al., 2014). In support of the separate-system view, work that examined sequential (as opposed to statistical) learning suggested that the coding of two sequence streams does not accrue additional costs (quantified behaviorally) beyond what is necessary to code for a single dimension (Mayr, 1996). This supports the modular approach, in which separate processes code the regularity of different stimuli dimensions (see Goschke & Bolte, 2012; Mayr, 1996, for supportive behavioral data). Such findings have been interpreted within a framework in which sequential structures in different stimuli dimensions are processed by different modules (Keele et al., 2003). Consistent with this view, Bubic et al. (2011) found that different neural systems are involved in evaluating predictions regarding object identity, location, and presentation time. Other studies have shown that odd-ball (unexpected) auditory or visual events produce patterns corresponding to surprise or prediction error in respective sensory cortices (Kok et al., 2012; Mustovic et al., 2003; Todorovic, van Ede, Maris, & de Lange, 2011).

However, an alternative viewpoint emerges from neuroimaging work that suggests that predictions are mediated by a single fronto-parietal system that codes for both stimulus features and stimulus locations. For example, Egner et al. (2008) manipulated the validity of cues in a cue-target paradigm and found that more informative cues evoked higher activity in fronto-parietal regions, not only when cues informed about a future location, but also when they informed about a specific visual feature of the to-be presented item. Similarly, Cristescu et al. (2006) studied responses to cues that predicted either the semantic category of a to-be-presented word or its spatial location, and the authors identified a similar network to that reported by Egner et al. (2008), with greater activity for diagnostic cues.

Thus, in the current study we hypothesized that *i*) predictable location streams would be associated with reduced metabolic demands seen in lower BOLD signal (prediction-related saving) in visual cortex as compared to the no-regularity baseline, *ii*) that predictable category streams would result in reduced BOLD activity in lateral occipital cortex and fusiform, *iii*) that location regularity could produce increased activity in fronto-parietal systems linked to valid cuing. Finally, we did not have a precise prediction regarding the dual regularity condition. On the one hand, the increased predictability in that condition within both streams, should produce reduced activity when compared to baseline, if only because the location dimension itself is easier to track. On the other hand, the work by Egner et al. and Cristescu et al. strongly suggests there is a core system mediating cue-based prediction, in which case making both predictions could produce a bottleneck, seen in greater activity in the dual-regularity condition than the single-regularity conditions or alternatively, as an “annulment of saving” that the latter offer as compared to baseline.

2. Methods

2.1 Participants

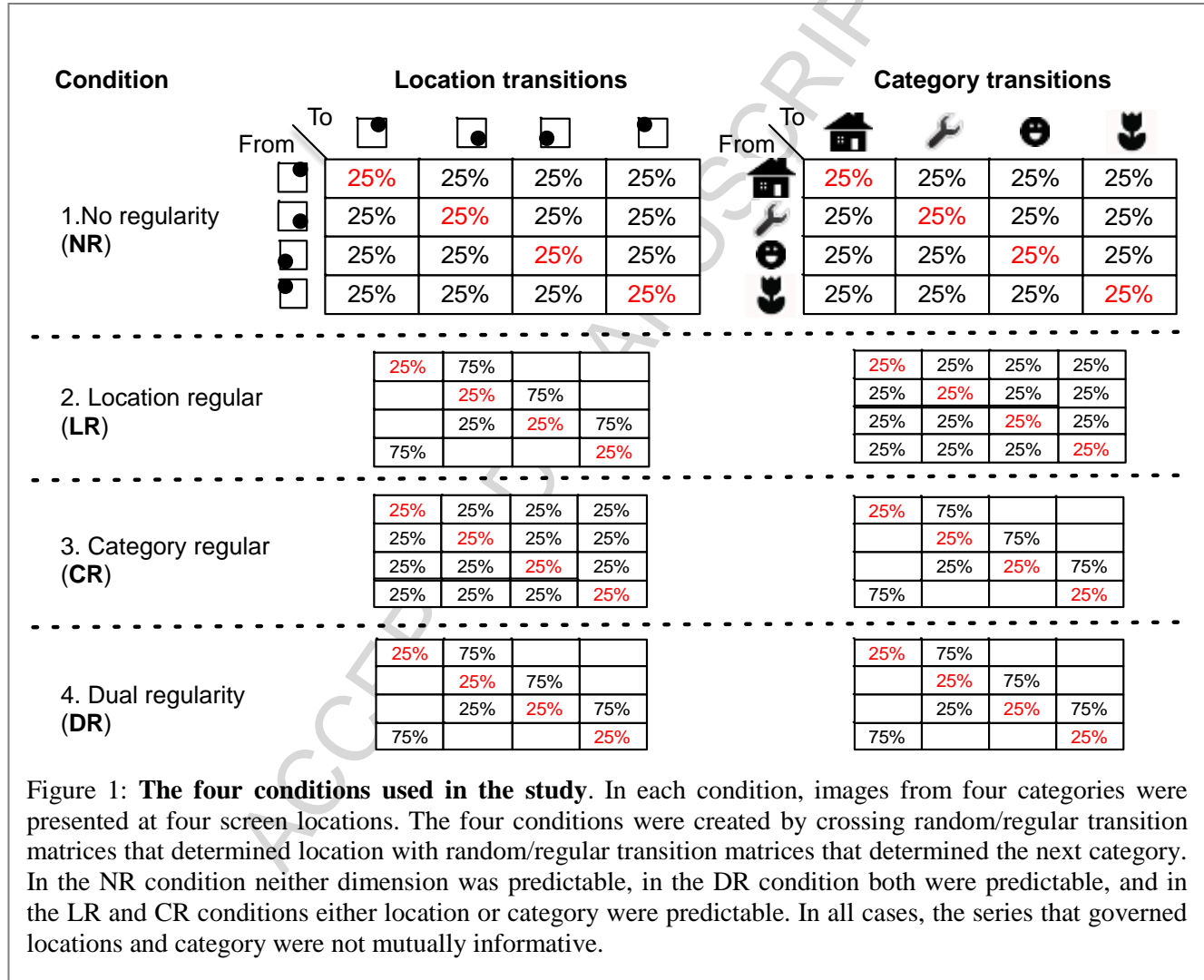
Twenty-five right-handed participants ($M = 24.6$ y.o.a, $SD = 3.9$, 12 female) with no history of psychiatric or neurological diseases, and normal or corrected-to-normal vision, participated in the fMRI study. They underwent an interview with a board-certified M.D to evaluate exclusion criteria and provided informed consent. The Ethical Review Board of the University of Trento approved the study and all participants provided informed consent prior to their participation. All participants were debriefed following their participation.

2.2 Materials, procedure and task

The stimuli were unique color images showing exemplars from the four categories: faces, flowers, houses and tools. Images were collated with permission from multiple databases and collections: faces from the colored neutral-expression collections (all age groups) from the Center for Vital Longevity Face Database (Minear & Park, 2004); flowers from the image-net.org synset; houses and tools from a collection culled from the internet. All images were unique as verified manually and through image matching software (DupDetector, <http://www.keronsoft.com/dupdetector.html>).

The experiment entailed looking at series of images. The structure of each series was determined by two factors (see Figure 1): *i*) location transition constraints for successive images, and *ii*) category transition constraints for successive images. There were four possible locations in the screen quadrants and four semantic categories from which unique image exemplars were drawn: faces, flowers, houses and tools. The transition constraints that governed the location or category regularities were either *low* (no constraints) or *high* (relatively strong constraints, but still stochastic). In the low-regularity case (formally, a random process), any of the four possible transitions within a dimension was equally probable, including a repetition of an image location or category. With high-regularity there was a 75% probability for specific location or category transitions and a 25% probability for repetitions. In the location dimension, high regularity transitions were: top-left \rightarrow top-right \rightarrow bottom-left \rightarrow bottom-right \rightarrow top-left, etc. In the category dimension, high probability transitions were: face \rightarrow flower \rightarrow

house → tool → face, etc. These transition mappings were maintained throughout the experiment. Note that the transition structure was generated separately for the locations and the category transitions so there was no mutual information between the input streams; i.e., learning and prediction about each stream could only be achieved if that stream was tracked, even in the condition when both streams were regular (dual regularity; see Figure 1).



Series were presented in one randomized assignment to all participants. A trial consisted of a central fixation circle (483ms) followed by the image screen (333ms) for a total trial duration of 816ms. Each series consisted of 49 trials. Images were presented via a projector with a 60Hz refresh rate and were observed via a headcoil-mounted mirror. The apparent screen distance was 135cm, image size was 4.5° x 4.5° and the center of each image was 4.95° from center. There was a distance of 7° between images.

The fMRI experiment comprised 5 runs, each 8min in length. Each run included 8 series: 2 series of each of the 4 conditions, for a total of 40 series. Each run began with a 15.4s fixation screen to allow for T1 stabilization effects. Each of the 8 series in the run was preceded by a 2.7s screen displaying the instruction 'READY....'. The series was then presented as a block lasting 39.5s. Participants were

instructed to simply observe the images and be prepared to click when prompted after each series, to show they are still alert. Following each series, there was 19s presentation of the fixation cross. The presentation of the cross was interrupted at a jittered period between 2 and 6 seconds after the onset by a red 'CLICK NOW' instruction which stayed on screen for 2s or until participants had responded. This prompt was included to maintain and evaluate alertness during the study. These clicks were monitored in real time and participants alerted if not responding during the run.

2.3 MRI Acquisition

Images were acquired with a 4-T MRI scanner (Bruker Medical, Ettlingen, Germany) at the University of Trento, using a birdcage-transmit, 8-channel receiver head coil (USA Instruments, Inc., OH, USA). Two T1-weighted 3D MPRAGE structural images were acquired (1x1x1 mm³, GRAPPA iPAT=2, 5:36min each). One was optimized for optimal contrast between gray and white matter tissue (MPRAGE_CNR; TE/TR/TI/flip angle = 4.18ms/2700ms/1020ms/7°) and the other was optimized for signal to noise ratio in gray and white matter tissue (MPRAGE_SNR; TE/TR/TI/flip angle = 3.37ms/2500/1200ms/12°; Papinutto & Jovicich, 2008). These two structural images were aligned and averaged to obtain a structural image with high signal-to-noise ratio. For fMRI, single-shot EPI BOLD functional images were acquired using the point-spread-function distortion correction method (Zaitsev, Hennig, & Speck, 2004). Two hundred and thirty-six EPI volumes lasting 519.2s were acquired during each of the 5 functional runs (for 944 total volumes and 2,076.8s).

2.4 fMRI analysis

2.4.1 Image pre-preprocessing

fMRI preprocessing was carried out using FEAT (FMRI Expert Analysis Tool v. 6), part of FSL (FMRIB's Software Library; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). The first six volumes of every fMRI image were deleted. The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of 5mm FWHM; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s).

We implemented a strict control for motion effects. Confound matrixes were created using the dvars metric (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) using the *fsl_motion_outliers* tool. The dvars metric measures intensity differences between volumes adjacent in time after realignment (motion correction); i.e., it is a differenced time series of the motion vector. Volumes that exceeded a boxplot cutoff threshold of (1.5 x interquartile range) were included in a confound matrix to be excluded in the first level general linear model (GLM) as an effect of no interest. Such volumes accounted for a mean of 5.6% of the data. In this way, we excluded from further analysis the signal from volumes with large intensity differences relative to volumes adjacent in time. This method is

similar to excluding outlier time points from the regression model, but it does so without adversely affecting temporal filtering or autocorrelation estimations.

2.4.2 Normalization

The two SNR- and CNR-optimized structural images were averaged to create a single mean structural image used in all subsequent processing. This structural image was preprocessed using the `fsl_anat` script where they were: reoriented to MNI orientation (`fslreorient2std`), automatically cropped (`robustfov`), bias field corrected (FAST), nonlinearly registered to a whole brain MNI template (FNIRT), FNIRT-brain extracted based on the alignment to the whole brain MNI template, and finally segmented by tissue type (FAST) and subcortical structure.

Following the first level analysis regression model, we aligned the statistical maps to MNI space in a single transformation based on matrices generated in the following three steps: 1) Aligning each structural image to the first EPI image in each run (i.e., the first image of the 6 discarded acquisitions; the image with the strongest anatomical contrast) using a 3 degrees of freedom (translation-only) linear FLIRT alignment, 2) using boundary-based registration (BBR; Greve & Fischl, 2009) to co-register the first EPI volume to the bias corrected, FNIRT-based brain extracted, and segmented structural image, 3) nonlinearly aligning the bias corrected, FNIRT-based brain extracted structural image to the MNI template (12 degrees of freedom linear initial step followed by non-linear registration with warp resolution of 10mm).

2.4.3 Single-participant regression models

Single-participant analyses were conducted using FEAT (FMRI Expert Analysis Tool v. 6). GLM was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). The main analysis was conducted as a block design, with 4 regressors of interest: one for each of the four experimental conditions. These were 39.5 sec blocks, convolved with a gamma HRF. There was also one regressor modeling the click event. Regressors of no interest included the standard and extended motion parameters (6 standard regressors-- 3 translation, 3 rotation -- the derivatives of those, the squared version of the standard regressors, the squared version of the derivatives), and the dvars determined motion confound matrix which consists of a 1 volume event for any volume that exceeded a dvars boxplot cutoff threshold of (1.5 x interquartile range).

Our primary interest was the effect of regularity on stimulus bound responses. However, the presence of repetitions in our design constitutes a form of low-level regularity. In all conditions, the probability of repetitions (both location and category) was matched at 25% (see Fig. 1) To evaluate the impact of category or location repetitions in each of the four conditions we implemented a similar analysis that only differed in that it consisted of a larger number of regressors of interest, as we separately modeled location and category repetitions (and their temporal derivatives) as separate event types for each condition.

2.4.4 Group-level analysis

Second-level (group) analyses were conducted as follows. Beta estimates for all conditions estimated within each run were averaged within participants using a fixed effects model. All group analyses were then carried out using FLAME (FMRIB's Local Analysis of Mixed Effects, stage 1 and stage 2 with automatic outlier detection; Woolrich, 2008). All contrasts were thresholded at $Z > 2.3$, followed by a cluster significance threshold of $p = 0.05$ adjusted for multiple comparisons using the Gaussian random-field theory method (Worsley, Taylor, Tomaiuolo, & Lerch, 2004).

2.4.5 Region of interest analysis

In addition to the whole-brain analyses that used cluster-based family-wise error correction, we also focused on several specific subcortical structures using ROIs, given our specific hypotheses about their role in statistical learning, anticipation and evaluation of predictions. Subcortical regions of interest (ROIs) were defined using the Harvard-oxford subcortical atlas. Based on prior work on coding of regularity we selected the bilateral thalamus, caudate, putamen, pallidum, hippocampus and nucleus accumbens as regions of interest. These were selected based on prior work linking them to the coding of regularities (Haruno & Kawato, 2006; Reddy et al., 2015; Turk-Browne, Scholl, Johnson, & Chun, 2010). Subcortical ROIs were transformed from common MNI space to original space using the inverse of the transformation we derived to convert them from original space to MNI space. Mean signal change values in each ROI were extracted for each participant for each condition, by collapsing across all voxels in each ROI. Voxels with signal change estimates greater than 5% were excluded to alleviate possible impact of outliers. Statistical analysis were performed using R's linear mixed effects model package (nlme; Pinheiro, Bates, DebRoy, Sarkar, & Team, 2013). For each region, a 2 (category information) x 2 (location information) linear mixed effects model was conducted. Family-wise error was implemented using a false-discovery rate applied to all p values of main effects and interactions reported by the ANOVAs for these regions.

2.4.6 Post-hoc analyses

We conducted two analyses after observing the main results in order to better understand several aspects of activity organization in the brain regions identified. These consisted of a Psychophysiological interaction analysis examining the connectivity of areas that showed reduced activity in all predictable conditions, and a multivariate examination of brain activity patterns in those regions.

Psychophysiological interaction

In order to investigate the effect of category regularity on functional connectivity we performed psychophysiological interactions (PPI) analyses (Friston et al., 1997) with FSL. We conducted a PPI analysis separately for each of the four functional regions of interest that showed reduced activity in all 3 predictable conditions (as compared to baseline). Each PPI analysis was conducted as follows: the (demeaned) average time series served as the physiological variable. The psychological regressor was category regularity (-1 for no category predictability (the NR condition), 1 for category regularity (the CR condition)). The PPI regressor for each of the 4 PPI analyses was computed as the product of the demeaned functional region of interest and the zero centered psychological regressor. We also

included the location predictability and dual predictability conditions as regressors of no interest. All pre-processing, normalization, group analysis, and thresholding were identical to the regression analysis outlined above.

Prior to conducting the PPI analysis, we evaluated the correlations amongst the time series derived for the four seed regions, since high correlations practically guarantee similar PPI results for the different regions. For each participant we derived the 6 pair-wise correlation values amongst the 4 regions and examined those values at the group level. The highest average correlation was found between the ACC and R. PCG [$M = 0.43$, $SD=0.15$] and the lowest was between visual cortex and R. PCG ($M = 0.18$, $SD=0.1$), with a mean pairwise correlation of 0.28 for all 6 pairwise values. Thus, separate PPI analyses were licensed.

Multivariate analysis

In this analysis, we focused on four regions of interest defined by the fact that they all reduced activity in each of the regular condition (CR, LR, DR) as compared to the NR condition. For each participant we treated that activation in each cluster as an activation pattern and examined its correlation to activation patterns in the other conditions. This produced three pairwise correlation values (CR:LR, CR:DR, LR:DR). We Fisher-Z transformed these correlation values, and the resulting value (3 values per participant per region) were inserted into a repeated measure ANOVA. The ANOVA indicated whether there was a significant difference in correlation patterns across the three conditions. We note that in this analysis, the raw pair-wise correlation values between conditions are less theoretically meaningful. To the extent that the spatial distribution of local activity in a region of interest is determined by a non-specific factor (e.g., Gray matter concentration) then the distributed activity patterns across conditions will be highly similar even if computations are slightly different. For this reason, the analysis examines differences in pair-wise correlations (independent of absolute magnitudes).

3. Results

In reporting the results we first report the differences of each of the regular conditions (CR, LR, DR) in relation to the baseline condition (NR) using simple main effects. We then consider conjunctions of regularity effects, with respect to the NR condition. We then report analyses focusing on the interactions between the regularity of 'what' and 'where' attributes.

3.1 Contrasts against baseline condition

When compared to the No Regularity (NR; baseline) condition where no regularities existed for either location or category, all three conditions with regularity resulted in reduced activity levels. We did not identify any case where a condition that contained regularities showed greater activation than the NR condition. Figure 2 presents regions where the NR condition associated with greater activity than the CR, LR or DR conditions, also showing relative overlaps in reduced activation (see Table 1 for cluster descriptives). As the figure shows, the right superior frontal gyrus (SFG), ACC, and parts of visual cortex showed reduced activation for all three regular conditions compared to NR (white color; $CR <$

NR & LR < NR & DR < NR). In the temporal cortex, bilaterally, we found reduced activity for category regularities (green; CR < NR), and, on the left, there was also reduced activity for the DR condition (marked in green and blue). The left ACC showed reduced activity for location regularity (red and pink; LR < NR; [LR < NR] & [DR < NR]).

A left posterior midline cluster extending across the cuneus, lingual gyrus and parahippocampal gyrus (PHG) showed reduced activity for the LR and CR conditions but not the DR condition (marked in yellow; [LR < NR] & [CR < NR]). In general, location-predictability associated with reduced activity in dorsal aspects of pre- and post-central gyri bilaterally. The CR condition was also associated with reduced activity in visual cortex, covering the occipital pole and posterior fusiform. However, a direct contrast between the location-predictable and category-predictable conditions produced a null effect. In the discussion we mention possible reasons for this and similar prior findings.

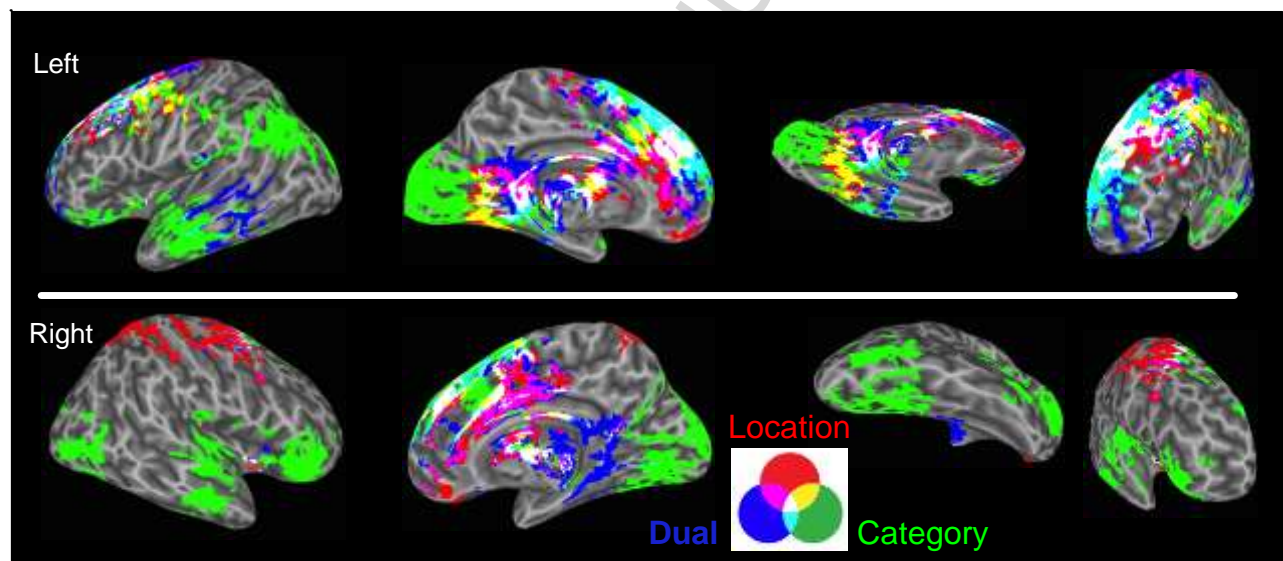


Figure 2: **Regions showing less activation for location-regular, category-regular or dual-regularity series as compared to the baseline no-regularity condition.** No brain region showed less activity for the no-regularity condition, in any of the three contrasts.

3.2 Frontal, occipital and basal-ganglia/thalamus show less activity in all statistically regular conditions

To identify areas where all three regular conditions showed significantly less activity than the baseline condition, we constructed a composite image, where each voxel was assigned the minimum T value of the three contrasts ($\text{Voxel_value} = \text{Min}_T([\text{NR vs. CR}], [\text{NR vs. LR}], [\text{NR vs. DR}])$), and this image was thresholded using standard cluster-based thresholding (see Methods; this analysis corresponds to identification of a “conjunction null” (Nichols, Brett, Andersson, Wager, & Poline, 2005) upon which we also perform cluster-based family-wise error correction). Thus, a significant cluster found for this composite image would indicate that in the given cluster all three conditions with regularity

significantly exceeded the necessary single-voxel threshold, so all three showed significantly less activity in the cluster compared to the NR condition.

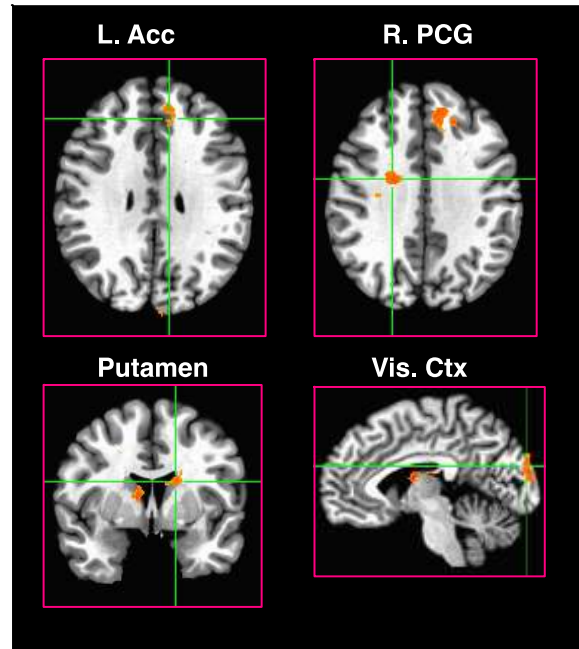
This analysis revealed four clusters: one in the anterior cingulate, one in occipital cortex, one in right PCG, and one in bilateral putamen extending into the thalamus. These locations match the areas shown in white in Figure 3, indicating that the overlaps found there are not attributable to a chance (see Table 2).

In each of these 4 clusters we calculated the between-condition similarity of multi-voxel response profiles in the CR, LR and DR conditions to answer the following questions: First, do these regularity-related decreases in activity simply reflect an overall mean fluctuation, while maintaining the multivariate pattern of activity in the regions across the three conditions with regularities; second, do the activity profiles in the DR condition more strongly resemble those of the LR or CR conditions, and thirdly, are the reductions in activity driven by the degree of attentional load, in which case responses in the LR and CR conditions should be most similar to each other.

For each participant we computed the pair-wise similarities between multi-voxel activation patterns in the three conditions, and then analyzed those on the group level after normalizing the correlation values using a Fisher-Z transformation. In the ACC, correlations were high (pair-wise mean Pearson's R values between .69 and .72) but did not differ across conditions. In the right PCG correlations were moderate (pair-wise means between 0.52 and 0.62) and without significant difference. In the subcortical putamen/thalamus cluster and in the occipital cluster correlations were moderate to high, and varied depending on condition-pair examined (see Figure 3b). For the subcortical cluster, a repeated-measures ANOVA on the Fisher Z-transformed correlation values showed a significant effect of condition-pair $F(2, 26)=3.89$, $p<.05$, as the

Regularity-related saving for DR, LR and CR conditions, and multivoxel similarity patterns

A: (NR > LR) & (NR > CR) & (NR > DR)



B: Two regions with significant differences in similarity of multivoxel response profiles

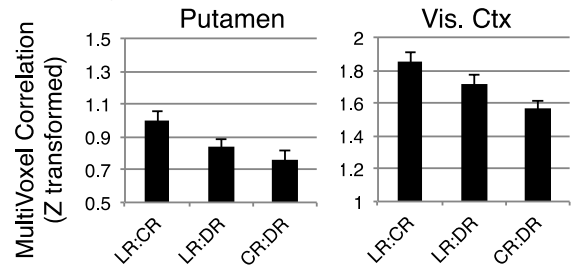


Figure 3. Areas where all three regular conditions were associated with reduced activity as compared to the NR condition. Panel A: location of the four clusters. Panel B: multivariate similarity patterns in two regions that differentiated the regular three conditions.

LR:CR correlation was strongest, and significantly differed from the CR:DR correlation $t(23)=2.54$, $p<.05$. A similar ANOVA applied to the correlation values in the occipital cluster revealed a similar pattern $F(2, 44)=3.99$, $p<.05$, with a significant difference between the LR:CR correlation and the CR:DR correlation $t(24)=3.54$, $p=.002$. To summarize, the four regions identified here showed reduced activity in each of the three conditions that manifested statistical regularities, but for the putamen and visual cortex we also found evidence of differential within-region organization, depending on the specific condition.

3.3 Sub-additive effects of dual predictability

We constructed an interaction term to probe whether the effect of category predictability depended on the presence/absence of location predictability. The interaction contrast $[NR - CR] > [LR - DR]$ identified 7 clusters (see Figure 4; the reverse contrast returned a null result). These included the left angular gyrus and lingual gyrus, and the right anterior cingulate extending to superior frontal gyrus, orbital gyrus and precentral gyrus, as well as visual region V1 and V2 (bilaterally). All these regions showed the same pattern: a lower activation for the CR than NR condition indicating reduced activity that is linked to category predictability (significantly so in R. orbital, L. angular, L. lingual, L. V1, R. ACC), but no category-related savings for the DR as compared to the LR condition. In fact, in several regions DR was associated with significantly higher activity than LR; specifically, R. PCG, L. lingual, R. V1-V2. To summarize, in a large set of regions category predictability was associated with lower activity only when location was not predictable. In addition, in all these regions, activity was above baseline for all four conditions indicating modulation of activation rather than deactivation.

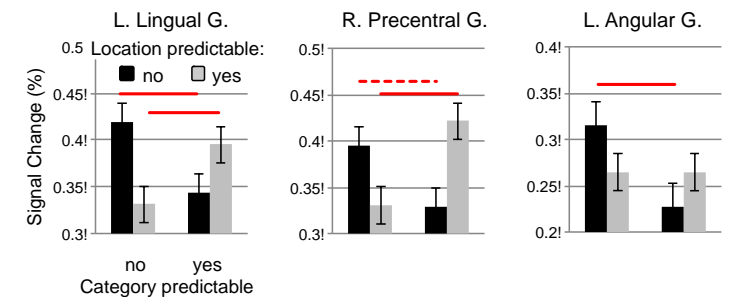
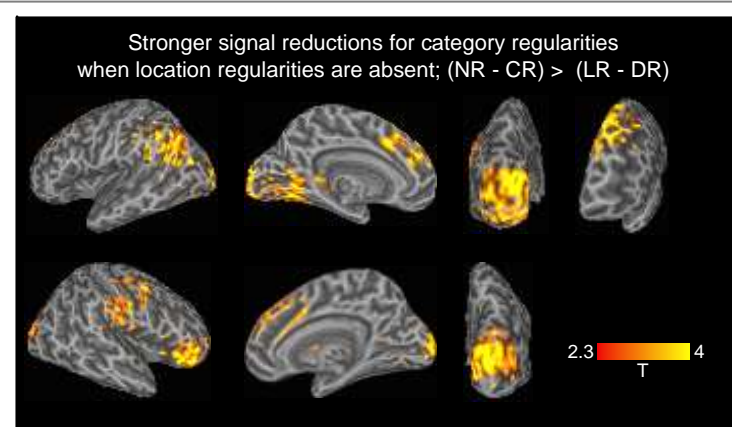


Figure 4. Areas where reduced activity related to category regularity depended on location regularity.

3.5 Regions showing lower activity for dual regularity than single regularity series

The above analyses were motivated by our hypothesis that dual regularities may be associated with processing costs or non-additive patterns of metabolic savings. Indeed, the BOLD data reported above show that the DR condition could be associated with greater activity than the CR condition or show a more subtle effect of annulling the potentially beneficial effect of category predictability. However, the additional processing load associated with dual predictions, may also be accompanied by facilitated processing in certain systems. In order to determine whether there were any regions that showed lower activity in the DR relative to both the LR and CR conditions we constructed a conjunction of the thresholded $DR < LR$ and $DR < CR$ contrasts (all contrasts were thresholded at $Z > 2.3$, followed by a cluster significance threshold of $p < 0.05$; see Methods). This identified a large cluster in the precuneus bilaterally. An examination of this cluster's absolute activation values showed that the DR condition associated with near-baseline values, whereas the other conditions showed above-baseline levels.

3.6 Repeats

In all conditions and series, repetitions of category or location occurred 25% of time. This allowed us to evaluate whether the context of regularity impacted the processing of repetitions, even though their marginal frequencies were identical across conditions. We compared location repeats in the LR to the NR condition, and category repeats in the CR vs. NR condition (see Table 3).

In the left inferior occipital cortex, location repeats were associated with less activity in the LR than NR condition. This cluster extends posteriorly to the right calcarine fissure and anteriorly to the posterior fusiform. However, location repeats were associated with greater activity in the LR than NR condition in the right middle frontal gyrus. For category repeats we found reduced responses to repetitions in the CR than NR condition in the left ventro-medial PFC.

3.7 Subcortical regions

Of the subcortical regions we examined (thalamus, caudate, putamen, pallidum, hippocampus, nucleus accumbens, all bilaterally), we found that all regions apart from the nucleus accumbens and right caudate showed sensitivity to location regularity ($p < .05$ FDR corrected for 36 tests; main effect of location, category and interaction tests for each of 12 regions). The modal pattern was lower activity for location regularity. None of the regions showed an effect of category regularity.

However, some regions (bilateral thalamus, bilateral caudate, left pallidum, and right hippocampus) further showed a location x category regularity interaction. These patterns are shown in Supplementary Figure 1. As can be seen, the modal interaction pattern was a significant effect of location regularity when category regularity was low, which was much more moderate or non-existent when category regularity was high. For the hippocampus, we found significant sensitivity to location regularity both when category regularity was high, and when it was low.

3.8 Psychophysiological interactions

Our analyses to this point showed that predictability was largely associated with reduced activity in areas mediating the orientation of spatial attention or access to semantic content, with no region showing increased activation in predictable contexts. We next examined whether the four core regions' decrease in activity was accompanied by an increase or decrease in synchronization with other brain

regions when category was predictable. This analysis was a post-hoc, non-planned analysis, but fundamental for evaluating whether the general pattern of decreased activity was accompanied by increased coupling between the identified regions and sensory cortices. Functionally, greater predictability could lead to increased coupling between these systems, while still being accompanied by reduced activity throughout the brain due to fewer cycles need to arrive at an ‘interpretation’ of the distal stimulus. We report our PPI results in terms of the beta coefficient reflecting the PPI effect. A positive coefficient corresponds to a regularity dependent increase in the coupling of the target region to fluctuations in the seed region.

For the ACC, R. PCG and the visual cortex cluster (but not the putamen), significant psychophysiological interactions were found. For the ACC seed region, negative Beta weights for the PPI regressor were found for right transverse temporal gyrus (TTG) and right insula. For the R. PCG seed region, we identified multiple regions with lower Beta weights for the PPI regressor, mostly in the right hemisphere: these included right superior temporal gyrus (STG), right inferior parietal lobule (IPL), postcentral gyri (bilaterally), right precuneus, right putamen and caudate, SMA, central part of cingulate gyrus, and lingual gyrus (V3), left middle and superior frontal gyrus. For the visual cortex seed region, we found an extended, mainly sensory network showing a negative Beta weight: these regions included PCG bilaterally, lateral STG and TTG bilaterally, posterior middle temporal gyrus bordering on V5 bilaterally, posterior cingulate/parahippocampal gyrus bilaterally, as well as right MFG, central part of cingulate gyrus, left putamen, left insula, left IPL, and left supramarginal gyrus (SMG). In all, we found a systematic pattern of decreased coupling in the CR condition.

4. Discussion

By manipulating the predictability of upcoming images’ location and semantic category, we were able to demonstrate effects of location regularity and semantic regularity and their interaction on brain activity. We found that location and category regularities, as implemented by transition constraints, reduced metabolic demands. All three conditions that contained regularities (LR, CR, DR) were associated with reduced activity not just in their respective sensory cortex but also in a common set of regions, supportive of a common system implementing regularity-related anticipation (specifically; visual cortex, ACC, putamen, R. PCG). Additionally, we identified activation patterns that were consistent with a processing bottleneck in certain systems: for certain areas category regularities only produced savings when not accompanied by location regularities. Finally, the LR and CR conditions produced patterns of reduced activity consistent with predictive processes related to saccade planning and access to category information. However, a direct contrast of these two conditions failed to reveal any regions with significantly different activity.

4.1 A common system for category and location regularity

The fMRI data identified a set of regions that showed reduced activity for all regular conditions in relation to the no-regularity baseline: dACC/vmPFC, primary visual cortex, the right PCG, and a dorsal striatal cluster spanning the bilateral putamen caudate and thalamus. Several of these regions have been repeatedly implicated in sensitivity to regularity or uncertainty.

In humans, the volatility of the environment correlates with dACC activity (Behrens et al., 2007), and ACC activity has also been linked to the coding of environmental uncertainty (Harrison et al., 2011). In studies of perceptual learning absent of a decision component, the ACC has been linked to rapid coding of uncertainty in auditory or visual stimuli (Nastase et al., 2014), and ACC connectivity with an extended network of brain regions further varies with uncertainty of auditory tonal series (Nastase et al., 2015). A meta-analysis of 9 studies of brain responses to uncertainty (White, Engen, Sorensen, Overgaard, & Shergill, 2014) identified the anterior cingulate, insula, dorsolateral prefrontal cortex and posterior parietal context as showing increased activity in contexts of greater uncertainty.

The striatum has long been implicated in learning (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007), and connectivity between the ventral and dorsal striatum is essential for learning (Belin & Everitt, 2008). In a study by den Ouden et al. (2009), the putamen (and dorsolateral prefrontal cortex) have been implicated in the acquisition of cue-target learning over time as modeled by a Rescorla-Wagner model, and shown to be sensitive to unexpected outcomes even when those are task irrelevant and learned incidentally, as is the case in the current study. The putamen has been traditionally linked to motor-sequence learning and execution via a cortico-striatal loop that connects the SMA, putamen, pallidum and thalamic nuclei (Graybiel, 1998). However, it has also been linked to artificial grammar learning absent of motor execution (Lieberman, Chang, Chiao, Bookheimer, & Knowlton, 2004; McNealy, Mazziotta, & Dapretto, 2006) as well as to auditory anticipation for known materials (Leaver, Van Lare, Zielinski, Halpern, & Rauschecker, 2009). Thus, we take the involvement of these regions in the current study to reflect the coding of overall uncertainty, or successful learning of input contingencies.

Another possibility is that regular sequences contained more predictable (non-salient) stimuli, so they were less 'attention grabbing.' Consequently, the differences identified in this set of brain areas would reflect the mean salience of the stimuli. However, a core finding in that neuroimaging literature is that stimulus saliency effects, as seen e.g., in the oddball vs. standard contrast, are localized in quite different areas (ventral attentional networks), which involves the SMG bilaterally and anterior insula (see, Downar, Crawley, Mikulis, & Davis, 2002, for findings in different modalities, and Kim, 2014, for meta-analysis). In addition, stimulus surprisal *per se* has been linked to activity in IPS and SFG (Strange et al., 2005). Thus, the set of regions identified here is less consistent with the possibility they were involved in computing the mean surprisal of series-stimuli.

While the ACC and putamen are likely linked to coding of uncertainty, associative learning or evaluation of outcomes in relation to a prediction, prior work suggests that reduced activity in visual cortex may reflect the reduced prediction error associated with location and category predictions. In a study that manipulated the frequency of left/right screen-side presentations of simple visual stimuli, presentation of stimuli on the *unexpected* side resulted in increased activity in V1 in a condition demanding no attention or evaluation of the stimuli (Kok et al., 2012). In another study where auditory tones predicted presence or absence of visual stimuli (den Ouden et al., 2009), surprising events -- either unexpected presentations or omissions of visual stimuli -- resulted in increased activity. Thus, the reduced activity we found could be due to the fact that the category- or location-regular conditions

were more frequently associated with confirmed predictions (i.e., a lower mean prediction error throughout the block of trials).

When examining the connectivity patterns of these regions we found that the ACC, R. PCG and visual cortex all showed lower connectivity with multiple brain regions in the CR vs. NR condition. The predictability of an input stream is known to impact connectivity in certain systems. For instance, predictability of auditory streams produces stronger connectivity between ACC and both frontal and occipital regions (Nastase et al., 2015). In addition, simply anticipating a particular semantic category by monitoring for it in an input stream has shown to increase connectivity between frontal and occipital regions (Summerfield et al., 2006). Given that our paradigm relied on extended series where transitions could be learned with high accuracy over time (and predictions could, optimally, be correct 75% of the time), the lower connectivity seen here for the CR condition could reflect the outcome of more precise predictions. Within several theoretical approaches, correct predictions would be accompanied by fewer processing cycles between high- and low-level regions for arrival at the correct interpretation of the external stimuli (e.g., Friston, 2009; Grossberg, 2009).

We note that while these regions commonly showed below-baseline activation, the internal organization of activation in the putamen and V1 clusters did vary across conditions as indicated by a multi-voxel analysis examining similarity of activation patterns across conditions. In both, activation patterns were most similar for the CR and LR conditions, and least so for the CR and DR conditions. This suggests that in these two regions, increased regularity was not associated with a uniform mode of processing, but one that was condition-sensitive.

4.2 Location regularities

For location regularity alone, we observed decreased activation in a cluster centered on the motor cortex, extending anteriorly to the bilateral MFG and ventrally to the IPS. This cluster corresponds broadly with the dorsal frontoparietal network for endogenous control of spatial attention (Corbetta & Shulman, 2002). As noted previously (Summerfield & Egner, 2009) differentiating the effects of prediction and attention is quite difficult. However, Kok et al. (2012) demonstrated it is possible to differentiate the two by showing that predictable stimuli (in visual cortex) tend to produce less activity when the stream is unattended, but greater activity when the stream is attended to. Thus, whether a certain cortical system shows reduced or increased activity to predictable stimuli (vs. unpredictable) may itself depend on attentional state.

Utilizing information provided by valid cues is a function that has been associated with the same fronto-parietal system identified here, but in a markedly different manner. Egner et al (2008) manipulated the diagnosticity by which cues predicted the upcoming location and found that more diagnostic cues (as compared to less diagnostic or completely non-informative cues) were associated with *increased* activity in the fronto-parietal system we identified (compare their Figure 2A, our Figure 2). The fact that we find less activity in this system for predictable series may point to a difference between computations elicited by exogenous cuing on the one hand, and endogenous learning-based predictions on the other. Note that our predictive conditions, by definition, had higher mean cue information (i.e., on average, cues reduced much more information in the predictable series). Yet, mean

activity in this fronto-parietal system was lower in the LR than NR condition. We are not aware of prior work where endogenous cueing resulted in decreased activation of this network. However, in a study of decision-making under uncertainty (Huettel et al., 2005) activity in the IPS has been shown to decrease in more predictable binary series (consistent with our findings). In addition, White et al. (2014) conducted a meta-analysis of 9 studies that manipulated uncertainty and concluded that more certain conditions associated with *lower* activity in ACC, Insula dIPFC and posterior parietal cortex, consistent with our findings. Thus, it may be that cue information (in attentional tasks) and overall series uncertainty drive this network in different ways.

An exception to this pattern were responses to location repetitions in the LR vs. NR conditions. Here, returning to a repeated location evoked greater activity in LR than NR, consistent with a surprisal effect. Note that in all conditions in the study, location repetitions constituted 25% of the trials (see Figure 1). Thus this effect can be strongly linked to violation of expectation. This was accompanied by reduced activity in lower level visual regions. One possibility to be evaluated in future work is that in the LR condition participants sometimes prepared saccades towards the anticipated location, and when surprised by a return, had to correct the movement, leaving less time to dwell on the image and consequently, reducing activity in low-level regions.

In conclusion, for location regularities, we find that they associated with a decrease in activity in a set of regions that closely resembles the dorsal fronto-parietal network for endogenous control of spatial attention. This decrease is consistent with the body of literature supporting predictive encoding (e.g., Friston, 2009; Mayrhauser et al., 2014; Rao & Ballard, 1999; Summerfield et al., 2008; Todorovic et al., 2011) and suggests that this system could benefit from reduced prediction error in the spatial domain. We conjecture that as the set of possible target locations becomes smaller the prediction error is resolved more quickly and efficiently, which produces less metabolic activation..

4.3 Category regularities

Category regularity was also associated with reduced activity in areas known to mediate access to conceptual knowledge as well as those linked to visual processing. For visual cortex, it could be that reduced BOLD is linked with shorter fixation durations (a typical finding for predictability in reading studies; Frisson, Rayner, & Pickering, 2005). We also observed a significant decrease in activation of the middle temporal cortex and bilateral fusiform, areas who's activity has been strongly and consistently found to be related to the visual semantics of our categories (Grill-Spector & Malach, 2004). We also observed significantly reduced activity in left angular gyrus, left middle frontal gyrus, and bilateral orbital frontal cortex, areas that have been suggested to be involved in visual semantics (Gerlach, 2007) but that are outside of what is considered the core visual category-selective perception network. Interestingly these areas have been strongly implicated in the semantics of language (Binder, Desai, Graves, & Conant, 2009; Price, 2012), and there is evidence for a commonality of neural representations of words and pictures (Bright, Moss, & Tyler, 2004; Chee et al., 2000; Gates & Yoon, 2005; Shinkareva, Malave, Mason, Mitchell, & Just, 2011).

Decreased activation in the ventral stream for category regularities is consistent with a subset of the repetition suppression (RS) literature. Repetition suppression refers to the decrease in a BOLD

response found for repeated stimuli (Grill-Spector, Henson, & Martin, 2006). In support of a predictive coding explanation, RS in the visual domain has been shown to be stronger when repetitions are more likely (Mayrhauser et al., 2014; Summerfield, Behrens, & Koechlin, 2011; Summerfield et al., 2008). On this perspective, sensory cortex may be primed in a top down manner, resulting in reduced prediction error, and more efficient processing. However, this result has not always been replicated (Kaliukhovich & Vogels, 2011; Kovacs & Vogels, 2014). Our findings speak to this issue as they too support the idea that a statistical regularity can result in more precise predictions and reduced prediction error. Our account further shows that predictions can be made at the level of abstract categories as all images in this study were unique and presented once. Consistent with this possibility, Fairhall et al. (2011) demonstrated repetition suppression to categorical representation of images. Here we extend this finding from repeated categories to expected categories.

Finally, we note that none of the subcortical regions we examined, including the hippocampus, showed sensitivity to whether there existed regularity in the category stream. This *prima facie*, appears inconsistent with prior work showing that the hippocampus responds to learned associations between stimuli of the sort presented here (Reddy et al., 2015; Turk-Browne, Scholl, Johnson, & Chun, 2010). However, a crucial difference is that in those studies the statistical relations were implemented in the form of a deterministic associative relation between two specific images. This, coupled with a much slower presentation rate, and tasks that demanded responses to each stimulus (in those studies) could have boosted hippocampal involvement in those studies.

Although the patterns for location regularity (NR – LR) and category regularity (NR – CR) differed qualitatively (Figure 2), we do not interpret these differential patterns as identifying separate ‘systems’. The direct contrast between the LR and CR conditions did not identify any significant difference. One possibility is that the coding of location regularities is accompanied by less organized activity in the semantic system (as compared to NR), and that the coding of category regularities is accompanied by less organized activity in areas specifically mediating location planning (as compared to NR). This would explain the somewhat non-intuitive result that both LR and CR differed from baseline, including in seemingly non-shared brain regions, but still did not significantly differ in a direct contrast. This is clearly an account that needs further investigation, but we note that a very similar pattern has been previously documented by Marois et al. (2000). In that study, a “standard” stimulus was presented repeatedly in the same location, interrupted by either infrequent location odd-balls (the standard image presented in another location) or identity odd-balls (another item in the same location as standard). The authors found that location odd-balls activated mainly the dorsal stream and identity odd-balls mainly the visual stream. However, a direct contrast between the conditions revealed very little differences (at uncorrected threshold).

4.4 Dual regularities

In the dual-regularity condition both the location and category streams were regular but composed of different series so that information from one stream could not be used to generate predictions about the other. Thus, optimal behavior could be achieved only if parallel predictions were derived from the two dimensions and integrated to create a detailed prediction regarding ‘what will be presented where’ on

the next trial. (Given the independent 75% probability for correct prediction of location/ category on each trial, a person continuously predicting would correctly predict both on ~ 50% of the trials in this condition).

The DR condition produced reduced activity in neural systems sensitive to location regularities and those sensitive to category regularities compared to the baseline NR condition. Qualitatively, these reductions in activity were moderate relative to the single regularity conditions. Few regions showed these kinds of savings for the DR condition but not the LR or CR conditions.

Most importantly, an interaction test identified a large set of regions where category regularities were associated with reduced activity when not accompanied by location regularities, but increased activity when accompanied by location regularities (i.e., $CR < NR$ showed reduced activity related to category predictability, but conversely $DR > LR$ showed an additional load with category predictability). This pattern was most robust in the left lingual gyrus and right PCG (see Figure 4). This “annulment of saving” pattern suggests increased computational load in the DR condition, and it rules out a simple model of purely additive savings because of regularity. The involvement of the right PCG is consistent with increased difficulty in prediction, as this region has been linked to explicit predictions of both visual and auditory attributes (Schubotz & von Cramon, 2002, 2004). There was one region in which the DR condition was associated with the least activity; the precuneus bilaterally. The precuneus is not traditionally associated with coding of temporally unfolding uncertainty, but it is often implicated in shifts in spatial attention or representation of high-level visual features.

It is again informative to compare these findings to those obtained in explicit cue-target paradigms. Egner et al. (2008) orthogonally manipulated cue informativeness with respect to item-location or a specific visual feature of an item. They identified a fronto-parietal system that tracked cue-predictability in both dimensions, and they did not find any evidence for an interaction between the two factors, suggesting that, “these sites harbor integrated but independent representations of spatial and feature-based search information.” (p. 6147). Our findings for the dual regularity condition show strong non-additive (interactive) responses (though mostly outside fronto-parietal regions, see Figure 4) and suggest that constructing predictions when licensed by two independent statistical streams can produce processing bottlenecks throughout the cortex.

Finally, the findings for the DR condition have implications for theories of brain activity in relation to stimulus entropy/uncertainty. In prior work, we and others have examined whether there are brain regions whose activity tracks overall input uncertainty (Harrison et al., 2006; Nastase et al., 2015; Nastase et al., 2014; Strange et al., 2005; Tobia, Iacovella, Davis, & Hasson, 2012; Tobia, Iacovella, & Hasson, 2012; Tremblay et al., 2013). However, the activity patterns found for the DR condition are largely inconsistent with an uncertainty-based explanation of brain activity. Formally, the uncertainty removed by each stimulus -- its information content or “surprisal” in a Bayesian sense -- was highest in the NR condition (4 bit/stimulus: 2 bits in the category stream and 2 in the location stream), mid-level in the CR and LR conditions (2.81 bit/stimulus: 2 bit in the unpredictable stream, 0.81 in the

predictable stream) and lowest in the DR condition (1.62 bits/ stimulus)¹. Thus, from an entropy-based approach, responses in the DR condition should have been either the highest or lowest of all conditions, if activity were to scale monotonically with uncertainty. In other words, our results are more consistent with the effect of predictability on stimulus bound responses - in which more predictable stimuli are processed more efficiently, resolving prediction errors more rapidly, but with potential bottlenecks when multiple predictions are licensed concurrently. This contrasts with a neuronal encoding of the predictability *per se* in terms of entropy or uncertainty about the stimulus before it appears.

4.5 Limitations and future directions

In the current work we aimed to study the natural, implicit process related to processing regularities. For this reason we avoided tasks that would explicitly focus participants on statistical structure, as such tasks impact responses to regular vs. irregular series (Aizenstein et al., 2004). We also avoided using a task demanding particular attention to the stimuli beyond passive viewing as attention to an input stream affects brain responses to predictable vs. non-predictable stimuli (Kok, Rahnev, Jehee, Lau, & de Lange, 2012). Consequently, we cannot say whether series with different regularity were uniformly attended, and in particular whether participants were less interested in regular series (thus accounting for the reduced activity). However, prior behavioral work suggests that if anything, regular streams draw greater attention than random ones. People prefer associative information (Trapp, Shenav, Bitzer, & Bar, 2015), in the temporal domain attention is biased towards regularities (Zhao, Al-Aidroos, & Turk-Browne, 2013), and visual statistical learning enhances (rather than detracts from) memory for elements in regular sequences (Otsuka & Saiki, 2016). Thus, prior work would suggest that that regular (though not deterministic) series of the sort used here are not typically associated with greater disengagement.

Another limitation of the work is that our analysis and interpretive approach implicitly assumes that participants' psychological response monotonically tracks the probability/surprisal of each stimulus (entropy being mean surprisal across the series). Behaviorally, it has been shown that stimuli that are neither highly predictable nor highly unexpected draw more attention (Kidd, Piantadosi, & Aslin, 2012, 2014), thus demonstrating a non-linear relation between probability and psychological response. Functional connectivity between certain brain systems also tracks regularity in an inverse-U shaped manner (Nastase, Iacovella, Davis, & Hasson, 2015). These sorts of effects dissociate psychological surprise from formal predictability, and, in the limit, may suggest that our more regular conditions could have been, at the same time, more attention grabbing. Similarly, it is likely that participants' responses at any given point do not reflect their coding of the stationary distribution from which the stimuli were drawn, but also reflect the impact of stimuli in the very recent past (Bornstein & Daw, 2012; Harrison, Bestmann, Rosa, Penny, & Green, 2011). Thus, participants' learning rate is a constraint that mediates the relation between the likelihood (predictability) of each stimulus and the psychological response to that stimulus, and this is an aspect we have not modeled in the current study.

¹ Shannon entropy of all series was 2 bits as they differed only in transition probabilities, not marginal frequencies. Markov entropy was 0.81 bit for regular streams and 2bits for the random ones.

Finally, due to absence of oculomotor measures in the study we cannot say whether part of these effects was related to the impact of condition on saccade performance or dwell time. It is possible that there were more eye movements in conditions where location was not predictable, which would result in greater activity in frontal and parietal eye fields. This would be consistent with the reduced activity in the LR vs. NR we reported. However, a prior neuroimaging study (Burke, Bramley, Gonzalez, & McKeefry, 2013) suggests that conditions that facilitate saccades do not necessarily result in reduced activity. That study contrasted saccades made on a predefined deterministic path to saccades made to random locations; it found that the deterministic condition was associated with faster, more accurate saccades as expected. Yet, this was accompanied by *greater* (rather than lower) activity in the deterministic condition as compared to the random. We also cannot exclude the possibility that decreased activity in low level visual cortices (in the CR condition) was due to reduced observation times of images due to a prior prediction (in fact we conjecture this is highly likely). That is, in the CR condition participants may have spent relatively more time observing the fixation cross and less time on the target image (there was constant input to visual cortex throughout the trial; what differed was the sort of input participants fixated on). However, this account would also predict more activity in visual cortex for location-regular conditions: Given the relatively short (333ms) image presentation time, prior knowledge of location could afford much longer observation times (taking into account 50-70ms saccade planning time, and additionally the time involved in saccade itself). This, *prima facie*, would also produce longer observation times in the location-predictable locations, which does not match the BOLD response profile that we observed. Obtaining accurate eye tracking data during such studies would be important to address these issues in the future.

4.6 Summary

We found that category regularity decreased activation in the ventral visual stream and semantic areas of lateral temporal cortex, whereas location regularity decreased activation in a dorsal fronto-parietal system implicated in the endogenous control of spatial attention. In addition, all predictable conditions produced lower activity in four brain regions indicating a core system sensitive to input regularity. But predictability can come with a cost: when regularities existed in both location and category dimensions, participants identified and used them for prediction, as evident by reduced activity in the dual regularity condition compared to baseline. At the same time, being able to predict both location and category resulted in an interaction indicative of a processing bottleneck; in several regions, category regularity only produced lower activity when location was predictable, but not when location was unpredictable. Most generally, our findings suggest that results obtained for single streams of information may not extend to multiple information streams, and that more predictable streams may not necessarily be the ones associated with least processing effort.

ACCEPTED MANUSCRIPT

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Condition

Location transitions

Category transitions

1. No regularity (NR)

2. Location regular (LR)

3. Category regular (CR)

4. Dual regularity (DR)

Figure 1

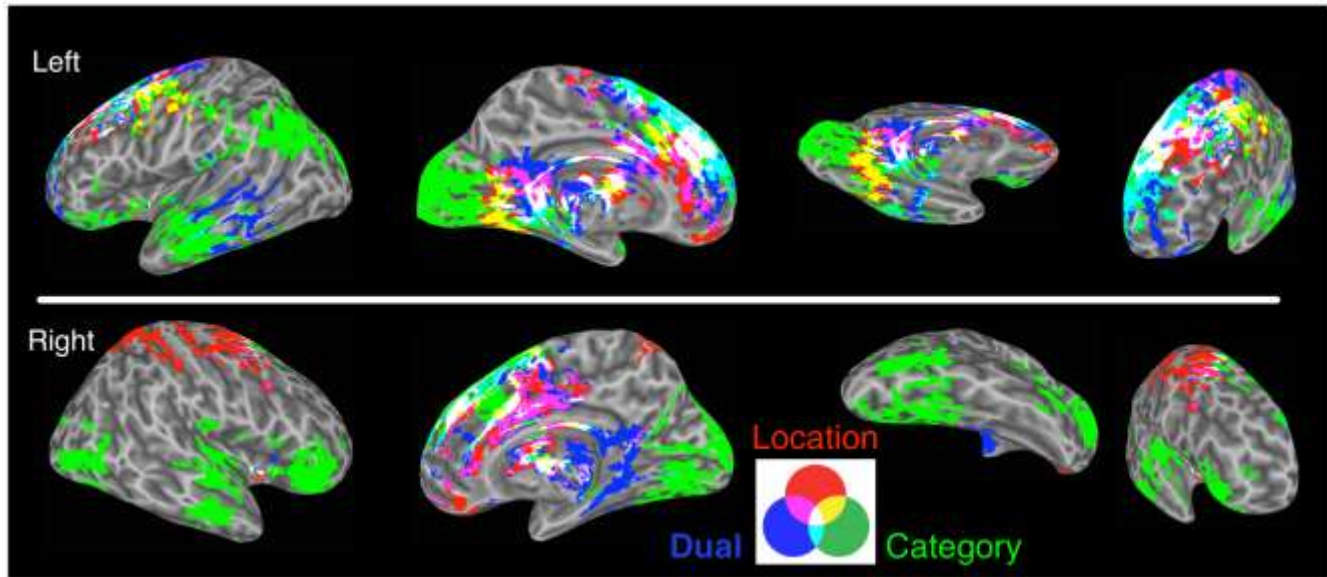


Figure 2

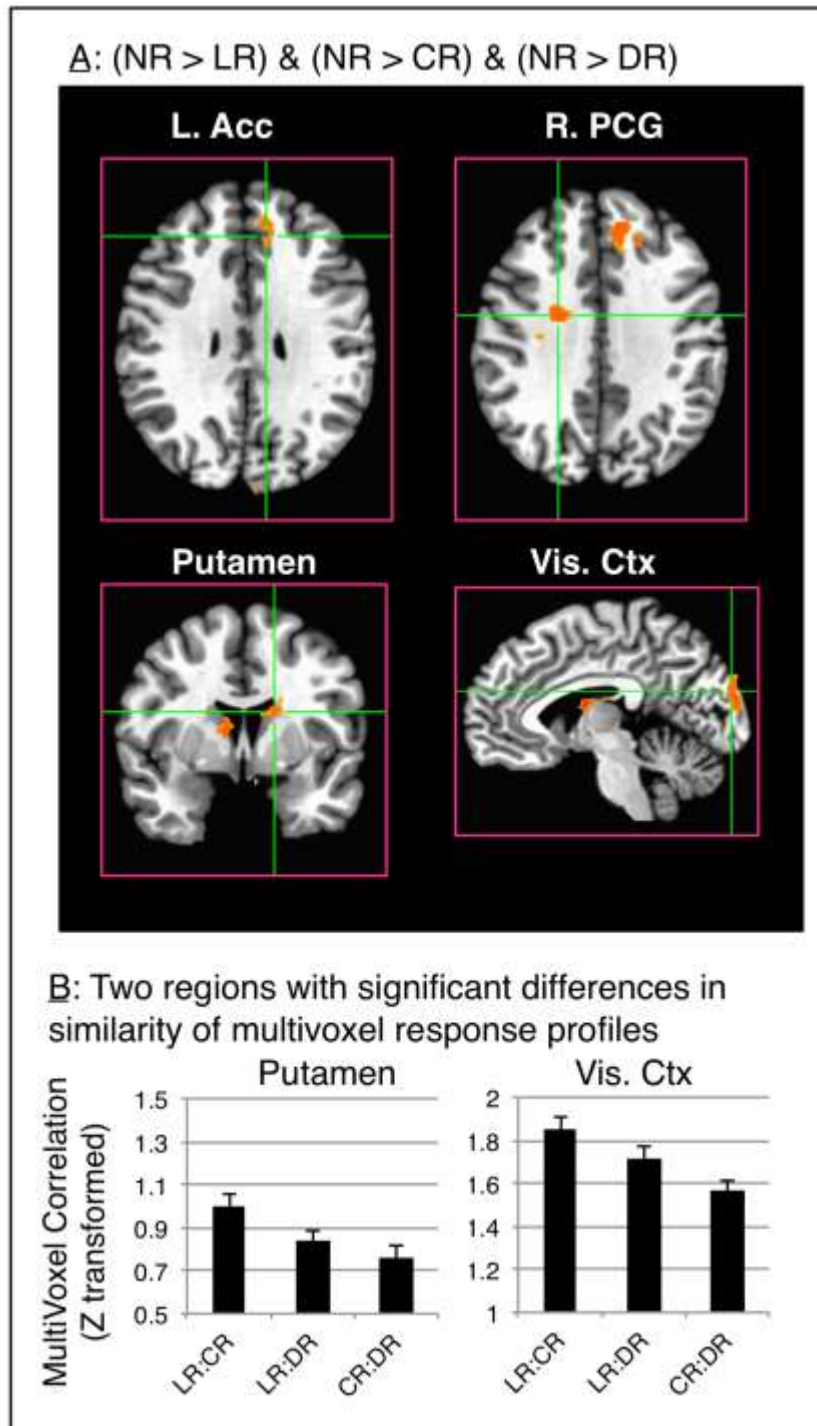


Figure 3

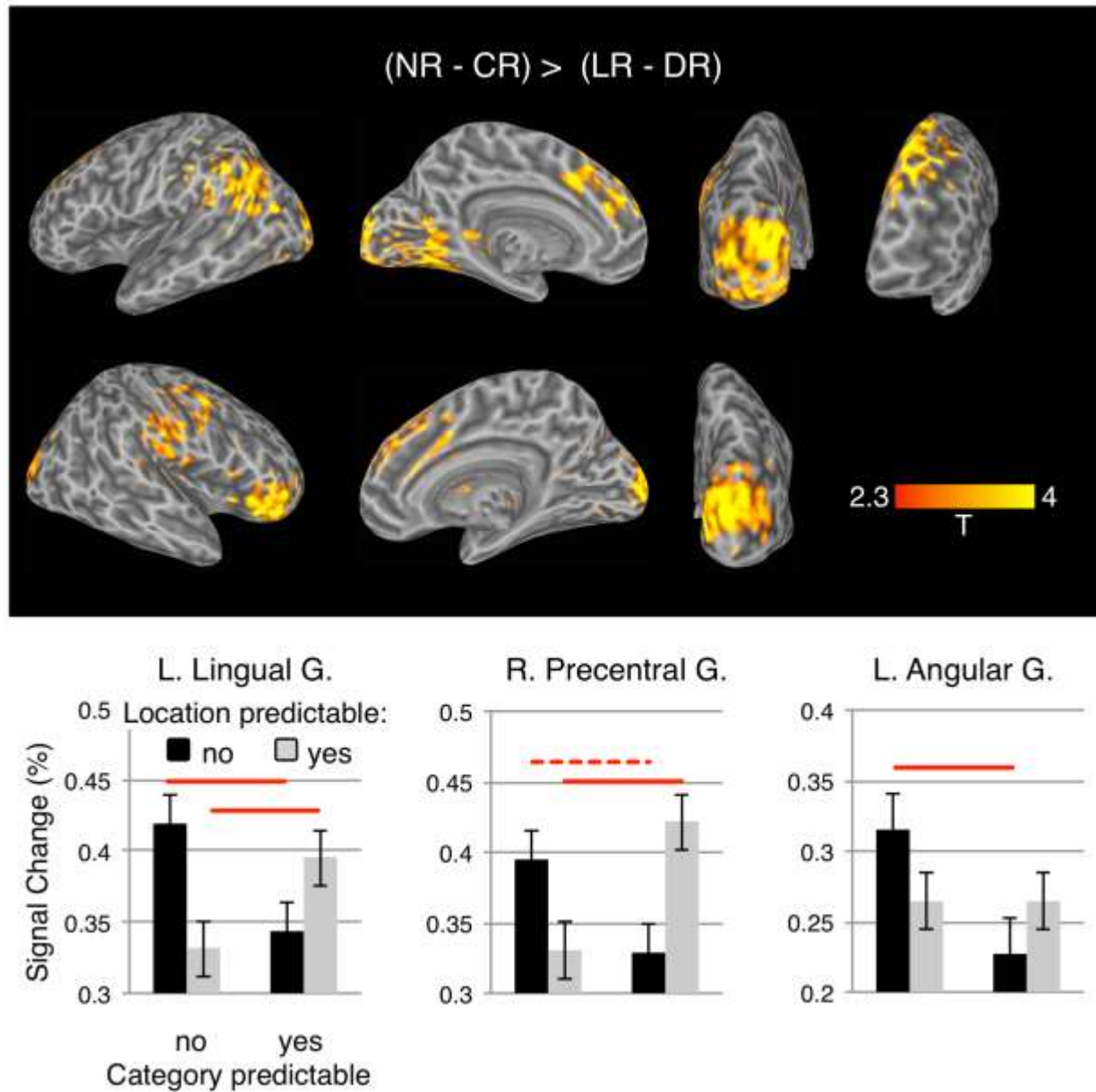


Figure 4

Table 1. Areas where conditions with regularities were associated with reduced BOLD signal

Cluster index	Volume [cc]	Max Zscore	MNI coordinates of Max			Center of Gravity [MNI]		
			X	Y	Z	X	Y	Z
<i>NR > LR</i>								
3	34.940	4.6	-2	45	-13	-3.77	9.74	30
2	6.070	3.67	-21	-61	-6	-19.8	-50.8	-1.51
1	3.481	3.94	19	-61	63	25.7	-48.2	57.9
<i>NR > CR</i>								
7	45.359	4.22	-67	-14	-23	-6.68	-69.2	0.721
6	37.262	4.68	-11	49	49	-11.4	25.4	43.6
5	5.456	5.15	-40	-64	44	-44.4	-59.6	33.9
4	5.315	3.87	-16	3	16	-0.853	-1.75	14.2
3	4.038	3.99	65	-9	-19	55.6	-14.9	-11.4
2	3.690	4.43	39	31	-7	43.7	30.5	-7.54
1	2.962	4.33	-43	22	-13	-42.4	23.1	-13.2
<i>NR > DR</i>								
3	27.316	4.08	13	-35	-9	2.3	-16.2	14.8
2	21.186	4.62	-15	39	45	-16.2	29.3	34.1
1	3.569	3.45	-46	-24	-13	-44.8	-31.8	-9.4

Table 2. Areas where all three conditions with regularity showed reduced activity compared to the no-regularity condition

Cluster index	Volume [cc]	Max Zscore	MNI coordinates of Max			Center of Gravity [MNI]		
			X	Y	Z	X	Y	Z
4	1.872	3.29	-11	35	20	-12	37.4	35
3	1.693	3.44	7	-2	2	-3.71	-2.73	14.5
2	1.328	3.18	20	-7	30	24.9	-5.57	36.7
1	0.829	3.4	-4	-99	7	-6.22	-96.3	18.8

Table 3. Effects of repetition

Cluster index	Volume [cc]	Max Zscore	MNI coordinates of Max			Center of Gravity [MNI]		
			X	Y	Z	X	Y	Z
<i>Condition Repeats (NR > CR)</i>								
1	4.816	3.49	-3	45	43	-2.56	38.9	51.1
<i>Location Repeats (NR > LR)</i>								
1	7.614	4.02	-35	-79	-16	-29.1	-84.8	-5.01
<i>Location Repeats (LR > NR)</i>								
1	3.799	3.45	28	50	29	26.3	46.4	32.4