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Novel response patterns during repeated presentation of affective and neutral stimuli

Ajay B. Satpute,[1] Lydia Hanington,[2] and Lisa F. Barrett[2,3]

[1]Department of Psychology, Pomona College, Claremont, CA 91711, USA, [2]Department of Psychology, Northeastern University, Boston, MA 02115, USA, and [3]Department of Psychiatry Harvard Medical School and Massachusetts General Hospital, Boston, MA 02115, USA

Correspondence should be addressed to Ajay B. Satpute, Department of Psychology, Pomona College, 647 N. College Way, Claremont, CA 91711, USA. E-mail: ajay.satpute@pomona.edu

Abstract

Repeated stimulus presentations are commonly used in social and affective neuroimaging tasks, but much remains to be known about how the brain processes such repetitions. Using functional magnetic resonance imaging, we found three groups of brain regions with distinct response patterns during repeated presentations of natural scene images. One group consisted of several limbic, paralimbic, frontoparietal and medial prefrontal areas and showed a habituation-like response across pleasant, unpleasant, and neutral image categories. A second group of occipital and adjacent posterior cortical regions showed a pattern of diminishing responses with repeated presentations of affective images but not for neutral images, and also plateaued to activation levels above baseline for all image categories. A third group involved bilateral frontopolar areas and the precuneus and exhibited a novel, non-monotonic response pattern. Activity was low on the first presentation, peaked upon the second presentation (first repetition) and subsequently diminished. These findings indicate that the transition from novel to increasingly familiar, and also arousing to less arousing, involves a broad array of neural mechanisms alluding to both passive learning and active inference strategies.

Key words: fMRI; repetition; habituation; novelty; arousal; multivariate

Introduction

Research in psychology and neuroscience relies heavily on the simple repeated presentation of stimuli (RP) to study a broad variety of phenomena. In clinical research, RP serves as a form of emotion regulation, as in exposure therapy (Abramowitz *et al.*, 2011). In social psychology, stimuli made familiar through repetition can influence social preferences, attitudes and judgments of affective experience (e.g. Maslow, 1937; Zajonc, 1968; Berlyne, 1970; Reber *et al.*, 2004; Moriguchi *et al.*, 2011). In the cognitive neurosciences, RP underlies the study of novelty detection (e.g. Berlyne, 1958; Tulving *et al.*, 1996; Friedman *et al.*, 2001; Moriguchi *et al.*, 2011), incidental influences of memory (e.g. repetition priming, Dehaene *et al.*, 2001; Gold *et al.*, 2006), and is used for brain mapping inferences based on 'repetition suppression' or 'functional magnetic resonance imaging (fMRI) adaptation', in which brain regions showing reduced activity across repetitions of trials serves as evidence that said brain region are involved in processes triggered by that trial (Henson and Rugg, 2003; Grill-Spector *et al.*, 2006; Summerfield *et al.*, 2008; Kumaran and Maguire, 2009; Wilson-Mendenhall *et al.*, 2014). Relatedly, RP is also necessary for studying habituation (Harris, 1943; Thompson and Spencer, 1966; Groves and Thompson, 1970; Rankin *et al.*, 2009) which, at least in theory, is considered fundamental for adaptive behavior. For instance, without habituating rodents may not overcome initial defensive responses when placed in a novel environment, thereby preventing an exploration of the area for resources. In like fashion, people may continue to show the same attentional interest or affective response to already well-known people, foods, music, objects, etc., potentially preventing us from moving past our 'gut feelings' and from seeking out new experiences (e.g. Oakes

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et al., 1991; Dijksterhuis and Smith, 2002). Relatedly, habituation is considered important for preventing "stimulus overload", in which stimuli are not discriminated on the basis of salience or novelty due to oversaturation (e.g. Kleinhans et al., 2009).

Such ubiquity underscores the importance for understanding the neural mechanisms that underlie RP. Human neuroimaging studies have shown that repetition of images (Breiter et al., 1996; Whalen et al., 1998; Phan et al., 2003; Ishai et al., 2004; Somerville et al., 2004; Yamaguchi et al., 2004; Johnstone et al., 2005; Hooker et al., 2006; Kumaran and Maguire, 2009; Moriguchi et al., 2011), sounds (Pfleiderer et al., 2002; Mutschler et al., 2010), odorants (Poellinger et al., 2001) and cutaneous stimulation (Becerra et al., 1999)—all show diminishing responses in brain regions such as the amygdala, and also the hippocampus (Tulving et al., 1996; Vinogradova, 2001; Fischer et al., 2003; Murty et al., 2013). Parallel findings have been observed in event-related potential studies with RP of affectively arousing stimuli in humans (Opitz et al., 1999; Olofsson et al., 2008; cf. Puce et al., 1999). These findings are built upon more direct cell-recording measures of neural activity in non-human animals, which have shown that neurons in the amygdala and hippocampus show diminishing firing rates with RP (Nishijo et al., 1988; Bordi and LeDoux, 1992; Vinogradova, 2001; cf. Wilson and Rolls, 1993).

Despite this work, findings in the human neuroimaging literature on RP have also been limited in two main ways. First, apart from a few notable exceptions (e.g. Opitz et al., 1999; Wright et al., 2001), prior work using fMRI has focused on only a handful of brain regions as being important for RP, such as the amygdala and the hippocampus. However, drug and genetic intervention studies in rodents have implicated at least four neurotransmitters systems in habituation (Leussis and Bolivar, 2006), and neuropsychology studies have implicated frontal and inferotemporal cortical areas as also playing a role in habituation and novelty (Bagshaw et al., 1965; Knight, 1984; Poucet, 1989). This suggests that several other brain regions may be involved during RP than is typically the focus of inquiry in prior neuroimaging work. And second, neuroimaging studies have, by and large, searched for response profiles that resemble behavioral habituation responses—that is, monotonically diminishing activity with RP. Yet, research in non-human animals suggests that neural responses related to RP may be more complex than simply paralleling the behavioral response profiles (Vinogradova, 2001; Leussis and Bolivar, 2006). For instance, although some neurons rapidly habituate to baseline firing rates with repeated presentations, other neurons never fully habituate and instead plateau to levels above baseline, and still others show a diminished response on the first presentation followed by gradual "disinhibition" or return to baseline (Vinogradova, 2001). Most of the aforementioned fMRI studies performed analyses across blocks of trials (e.g. separating them into "early" and "late" phases) or comparing novel with well-familiarized stimuli, and thereby cannot examine these dynamics occurring across RP.

Taken together, many brain regions may relate to RP but might have been overlooked in prior neuroimaging work if their response profiles were not monotonically diminishing. In this study, we used a more flexible analytical approach that imposes minimal constraints on the response patterns that occur across RPs (e.g. Gonzalez-Castillo et al., 2012; Neta et al., 2015). Participants viewed RPs of affectively arousing and neutral natural scene images (Lang et al., 2008) while undergoing fMRI. Activation clusters that were responsive to the experimental factors (RP and affect category) were identified—but without stipulating particular response profiles—by performing an analysis of variance (ANOVA). Activation clusters were then grouped together on the basis of their response profiles using *k*-means clustering to simplify the findings by data reduction and to emphasize patterns that are shared across multiple activation clusters. We examined whether activation clusters organized into a single group sharing a monotonically diminishing response with RP, or multiple groups, perhaps depending on the affect category of the stimulus or the dynamics of the response across RPs.

Based on prior work, we expected the amygdala and hippocampus to show reduced activity with RP regardless of their affective quality, as suggested by prior studies (Nishijo et al., 1988; Bordi and LeDoux, 1992; Moriguchi et al., 2011). But to formulate broader hypotheses that incorporate additional brain regions, we turned to fMRI research on the functional connectome. Such work has found that brain activity organizes into several large-scale 'intrinsic' networks on the basis of correlated activation patterns over time (Power et al., 2011; Yeo et al., 2011). For example, the amygdala participates with several limbic, paralimbic and insular brain regions that together comprise a so-called 'salience' network (Seeley et al., 2007), on the basis that many of the brain regions in this network are engaged by tasks manipulations involving affect (Barrett and Satpute, 2013; Satpute et al., 2015b; Lindquist et al., 2016) and may direct attention accordingly (Vuilleumier, 2005; Touroutoglou et al. 2012). Using our data-driven analytical approach, we first examined whether activation clusters grouped together on the basis of their response profiles with RP, and subsequently, whether they tended to overlap with the salience network. In like fashion, we also examined whether other activation clusters responsive to RP were organized on the basis of functional networks. Of interest is activity in brain regions implicated in visual processing, which have been organized into a "visual network" involving the occipital cortex and adjacent posterior cortical areas (Yeo et al., 2011). Brain regions in this network show greater activity when presented with affectively arousing *vs* more neutral visual stimuli (Lang et al., 1998; Vuilleumier, 2005; Satpute et al., 2015a), but also continue to respond even after dozens of stimulus presentation (Schupp et al., 2006). Accordingly, the response profile in these areas may on the one hand diminish for affectively arousing stimuli as their arousing quality diminishes with RP, but on the other hand may continue to respond at levels above baseline. We also used our exploratory analysis to search for novel response patterns across activation clusters, given the evidence that RP likely involves an extensive set of brain regions (Leussis and Bolivar, 2006) and more complex response profiles than simply recapitulating behavioral habituation responses (Vinogradova, 2001).

Methods

Participants

Thirty healthy, right-handed subjects consented to participate. (16 female, 14 male; age range = 19-36 years). Participants were excluded if they had contraindications for the MRI environment (presence of ferromagnetic metals in the body), were claustrophobic, pregnant, or had a history of psychiatric or neurological illness. Study procedures were approved by the Massachusetts General Hospital Institutional Review Board.

Stimuli and procedure

Participants were presented with four negative (averaged normative valence = 2.80, arousal = 5.72; image identification numbers: 3030, 7380, 9320, 9582), positive (averaged normative

valence = 7.41, arousal = 5.33; image identification numbers: 2391, 1590, 8200, 5910) and neutral (averaged normative valence = 5.65, arousal = 3.80; image identification numbers: 2214, 7080, 4100, 8250) images from the International Affective Picture System (IAPS). To reduce idiosyncratic differences across images categories, images in each affect category contained roughly similar characteristics as follows: each affect category contained one image involving human faces and an implied interaction between conspecifics, one image involving human faces but no implied interaction between conspecifics, one image depicting a behavior (e.g. motorcycle riding with no face visible) and one image without living organisms. During one functional scan, images were presented for 3.5 s, five times each, randomly arranged, with a jittered stimulus onset asynchrony of 4, 6, 8, or 10 s. Participants rated how aroused they felt in response to each image using a three-point scale (1 = "low", 2 = "mid", 3 = "high") while the image was on the screen. A brief practice session stimuli were completed before scanning to familiarize participants with the task. The practice used a separate set of stimuli but with similar levels of normative arousal and valence.

Apparatus and scanning parameters

Stimuli were presented using E-Prime experimental software (Psychology Software Tools, Pittsburgh, PA) on a PC. Images were projected onto a screen in the magnet bore made visible by a mirror mounted on a head coil. Foam cushions were used to reduce head motion and scanner noise was dampened using earplugs. Images were acquired using a Siemens Magnetom Trio Tim 3-T Magnetic Resonance Imaging system (Siemens Medical Systems, Iselin, NJ) equipped with a 12-channel gradient head coil. Structural scans included a high-resolution 3D MP-RAGE sequence (echo-planar imaging sequence, TR/TE/flip angle = 2.53 s/3.39 ms/7°, 1 × 1 mm in-plane resolution, 1 mm slice thickness). Functional scans were acquired using a gradient-echo T2*-weighted sequence (TR/TE/flip angle = 2.0 s/30 ms/90°, 33 coronal slices angled perpendicular to the AC/PC line, voxel size 3.12 × 3.12 × 5 mm, interleaved acquisition order). Four scans were acquired and discarded to allow for signal equilibrium. Signal dropout occurred in the medial orbitofrontal and ventromedial prefrontal regions (Supplementary Figure S1).

Data analysis

For behavioral data, mean arousal ratings and reaction times were calculated for each participant and submitted to a similar repeated-measures ANOVA to identify effects related to presentation and valence. Behavioral data were only available for 19 participants due to errors in data storage. As such, although sample averages are presented, we refrain from conducting additional results using arousal ratings.

For image analysis, images were co-registered, motion corrected, normalized (MNI-ICBM152 template), resliced (3 mm^3 voxels) and smoothed (6 mm FWHM) using SPM8 software. Statistical models were generated and estimated using NeuroElf software (www.neuroelf.com). First-level box-car regressors modeled image presentation durations separated by valence (positive, negative, neutral) and presentation (first through fifth). Regressors were convolved with a canonical hemodynamic response function (HRF). Motion parameters and a high-pass filter (80 s cutoff, discrete cosine transform) were also included in the model. For second-level analyses, subjects were modeled as a random variable and an AlphaSim MonteCarlo simulation (as implemented in AFNI) was used to select a combined height ($P < 0.001$) and extent ($k = 37$) threshold given a smoothness estimate (10.7 mm estimated from the data) to identify activation clusters that survived a whole-brain family-wise error (FWE)-corrected threshold of $P < 0.05$. An omnibus *F*-test was used to identify activation clusters that showed significant variability due to the 15 (3 valences × 5 presentations) conditions using the corrected threshold. For each subject, beta values for voxels within each activation cluster were averaged to generate subject-by-condition beta matrices for each cluster.

To identify common patterns across clusters and simplify the presentation of results, betas from activation clusters were submitted to a *k*-means clustering analysis (Matlab software; kmeans.m using the default "squared Euclidean distance" metric). Specifically, betas for each activation cluster were averaged across subjects and then *z*-scored within each activation cluster to prevent *k*-means clustering on the basis of grand means or arbitrary scaling. An elbow criterion with Calinski–Harabasz values was used as a stopping rule for identifying the number of groups. One leaf corresponding to a cluster that was not in grey matter was excluded from further analysis. To characterize response patterns in each group of clusters, betas were averaged across clusters and submitted to a repeated-measures ANOVA for which an omnibus *F*-test was calculated that assessed whether the variation between the 15 conditions (3 affect categories × 5 repeated presentations) was greater than the error variation within conditions. Follow-up polynomial contrasts for linear, quadratic and cubic effects are reported.

Given the data-driven nature of this study, we assessed reproducibility by calculating split-halves reliability for the overall *F*-test and the pattern of betas for cluster groupings. We randomly divided subjects into two subgroups. For each subgroup, we conducted a whole-brain *F*-test and extracted significant clusters at FWE-corrected levels. Given the significantly smaller sample size, we used a slightly more lenient voxel-wise threshold at $P < 0.005$, but a more stringent *k*-extent at $k = 86$ for an FWE-corrected level of $P < 0.05$. To be sure, thresholding for the split-halves samples was only used to identify activation clusters—or a set of spatial locations from that sample—that were then used to extract the average parameters estimates using data from the other sample. This procedure provides an estimate of the split-halves reliability of results and relatedly mitigates over-fitting and "double dipping" (Kriegeskorte *et al.*, 2009). We then submitted the extracted values to a *k*-means clustering algorithm (as above for the full sample), and assessed whether similar response patterns were observed. This split-halves procedure was conducted twice for a more thorough assessment. The second time used an orthogonal random assignment of subjects to subgroups relative to the first time.

Observed increases or decreases in activity with RP may be due to actual greater or lesser hemodynamic responses, or merely due to poorer fits of hemodynamic responses with the canonical HRF used in the GLM. Hence, time-course plots were also calculated for each of the 15 conditions to better understand the nature of observed response patterns related to RP. We implemented a modified finite impulse response model. A separate GLM was performed for each individual trial. The selected trial was modeled using eight "stick" functions, one for each time point beginning with the image onset, for a 16 s window. The remaining trials, motion parameters and temporal filters were modeled as in the initial GLM (i.e. the trials were nested in their respective conditions and convolved with the canonical HRF). After model estimation for the selected trial, we

extracted parameter estimates for each time point, and averaged them across voxels within each activation cluster, for each subject. This model was iterated for every trial in the experiment. To produce time-course plots, time courses were averaged across activation clusters that shared a cluster grouping and plotted with standard errors bars. We note that although the time-course plots may serve as useful converging evidence, however, they should also be interpreted with reservation because the rapid event-related design we used is not ideally suited for a time-course analysis.

It is possible that effects related to RP occur not only on the level of specific stimulus identities, but also across stimuli of the same affect category (i.e. generalizes across stimuli, within affect category). Hence, we tested whether habituation occurs across different images of the same valence category by including a parametric regressor to the first-level GLMs. To clarify, the first-level GLM included 15 regressors (5 presentations × 3 affect categories), with each regressor involving four distinct images. To each regressor, we added an extra parametric regressor that weighted each image in the order it was presented using a habituation-like response, or specifically: [3, 1, −1, −3]. We then examined whether diminishing responses occur across different stimuli, averaging across affect categories and presentations, at whole-brain, FWE-corrected levels ($P < 0.05$).

Results

Behavioral results

Behavioral data are tabulated in Table 1. A 3 (affect categories) × 5 (presentation order) repeated-measures ANOVA indicated that arousal ratings varied by repetition [$F(4, 72) = 4.58$, $MSE = 0.039$, $P = 0.002$]. Follow-up polynomial contrasts revealed a significant linear decrease in arousal experience with RPs [$F(1, 18) = 6.64$, $MSE = 0.029$, $P = 0.019$, partial $\eta^2 = 0.27$], but no higher order effects (P's > 0.05). There was also a main effect of affect category [$F(2, 36) = 88.61$, $MSE = 0.36$, $P = 0.012 \times 10^{-12}$]. Participants reported higher arousal ratings during negative images than both positive [$F(1, 18) = 56.56$, $MSE = 1.075$, $P = 0.0058 \times 10^{-5}$, partial $\eta^2 = 0.76$] and neutral images [$F(1, 18) = 218.56$, $MSE = 0.55$, $P = 0.016 \times 10^{-9}$, partial $\eta^2 = 0.92$], and also higher arousal for positive than neutral images [$F(1, 18) = 18.73$, $MSE = 0.52$, $P = 0.04 \times 10^{-2}$, partial $\eta^2 = 0.51$]. A similar repeated-measures ANOVA indicated that reaction times varied by repetition [$F(2.611, 47.003) = 10.738$, $MSE = 171\,715.46$, $P = 0.007 \times 10^{-4}$, Greenhouse–Geisser corrected]. Follow-up polynomial contrasts revealed a significant linear decrease in reaction time with RPs [$F(1, 18) = 24.038$, $MSE = 176\,727.78$, $P = 0.012 \times 10^{-2}$, partial $\eta^2 = 0.57$], but no higher order effects (P's > 0.05). There was also a main effect of valence [$F(2, 36) = 5.041$, $MSE = 69\,877.47$, $P = 0.012$]. Participants responded slower for positive images than neutral images [$F(1, 18) = 12.952$, $MSE = 105\,094.02$, $P = 0.002$, partial $\eta^2 = 0.42$]. There was no difference in reaction times for negative and positive images [$F(1, 18) = 1.402$, $MSE = 110\,783.7$, $P = 0.25$], or negative and neutral images [$F(1, 18) = 2.935$, $MSE = 203\,387.07$, $P = 0.10$]. Overall, the behavioral results indicate that participants made faster judgments and had reduced arousal with repeated exposures.

Neuroimaging results: individual activation clusters and group clustering

We first identified activation clusters that were responsive to the task conditions using a whole-brain omnibus F-test. Correlating F-test values across the whole brain showed good split-halves reliability for two orthogonal sampling splits (split 1, $r = 0.82$; split 2, $r = 0.83$). The omnibus F-test on the full sample revealed 73 activation clusters ($P < 0.05$, FWE-corrected). The coordinate-based summary of results is presented in Table 2. Bar plots of responses across the task conditions for individual activation clusters are presented in Supplementary Figure S2. Although many activation clusters showed monotonically diminishing response profiles, several also exhibited response patterns that did not appear to resemble a simple linear increase or decrease. Rather than stipulate-specific response patterns (e.g. only present results for areas showing habituation-like response patterns), our goal was to identify what other kinds of response patterns occurred with RP. As such, we used a data-driven, k-means clustering analysis to identify activation patterns that were common across several activation clusters. Such data reduction necessarily involves summarizing over potentially important differences for each individual activation cluster. Interested readers may refer to the Supplementary Material for examining the activation patterns for individual activation clusters. Three groups of clusters were estimated based on the elbow criterion using Calinski–Harabasz values (Figure 1D), and also from split-halves samples (Supplementary Figure S2).

Group 1: diminishing responses with RP for affective and neutral stimuli

Group 1 included clusters distributed across cortical and subcortical areas (Figure 2A and B). Cortical areas included dorsomedial prefrontal cortex, lateral orbitofrontal cortex, left anterior insula and ventrolateral prefrontal cortex, somatosensory cortex, inferior temporal cortex and lingual gyrus. Subcortical regions included the amygdala, hippocampus, caudate and cerebellum. Combining activity across activation clusters, a repeated-measures ANOVA revealed a main effect of repetition [$F(4, 108) = 12.14$, $MSE = 0.191$, $P = 0.035 \times 10^{-6}$]. Follow-up polynomial contrasts revealed a significant linear decrease over presentations consistent with a habituation interpretation [$F(1, 27) = 30.47$, $MSE = 0.084$, $P = 0.008 \times 10^{-3}$], but no higher order response patterns (P's > 0.35, for quadratic and cubic polynomials).

The main effect of affect category did not reach significance [$F(2, 54) = 2.46$, $MSE = 0.101$, $P = 0.095$]. Still, we conducted follow-up tests on affect categories given considerable evidence from prior studies that more affectively arousing stimuli evince greater activity in these areas (e.g. Hayes and Northoff, 2011; Sabatinelli *et al.*, 2011; Hayes *et al.*, 2014; Lindquist *et al.*, 2016). Greater activity was observed during high arousing/negative images than neutral images [$F(1, 27) = 6.15$, $MSE = 0.153$, $P = 0.02$]. But there was no difference in activity during the highly arousing negative and the moderately arousing positive images [$F(1, 27) = 0.425$, $MSE = 0.208$, $P = 0.52$], or between the moderately arousing positive and low arousing neutral images [$F(1, 27) = 1.87$, $MSE = 0.242$, $P = 0.18$]. The interaction between affect category and repetition was not significant [$F(8, 216) = 0.88$, $MSE = 0.118$, $P = 0.53$]. As shown in Figure 2A, Group 1 responded strongly during the first presentation images regardless of affect category, and decreased to no difference from a fixation baseline by the fifth presentation. To provide a descriptive account for how Group 1 brain regions relate with intrinsic networks, we examined the overlap between activation clusters in Group 1 with seven 'resting-state' network maps (Yeo *et al.*, 2011). Group 1 activation clusters fell in several

Table 1. Mean reaction times and arousal ratings across valence and presentation

Presentation	1	2	3	4	5	1	2	3	4	5
	Mean reaction times					Standard errors				
Unpleasant	1593	1386	1277	1323	1194	103	107	110	129	99
Pleasant	1609	1438	1302	1330	1296	109	105	126	118	124
Neutral	1501	1357	1241	1191	1086	95	111	117	99	90
	Mean arousal ratings					Standard Errors				
Unpleasant	2.42	2.37	2.45	2.33	2.38	0.08	0.07	0.09	0.09	0.08
Pleasant	1.68	1.66	1.54	1.49	1.58	0.09	0.07	0.07	0.06	0.07
Neutral	1.37	1.30	1.26	1.22	1.18	0.06	0.05	0.06	0.05	0.05

Note. Arousal ratings were made on a three-point scale from '1' = low to '3' = high.

networks including default, frontoparietal, dorsal attention and salience networks (Figure 3).

Group 2: greater diminishing responses with RP for affective stimuli

Group 2 primarily included occipital cortex and adjacent temporal, parietal and fusiform areas (Figure 2C and D). Combining activity across clusters, a repeated-measures ANOVA revealed a main effect of repetition [$F(2.83, 116) = 3.34$, $MSE = 0.456$, $P = 0.012$, Greenhouse–Geisser corrected]. Follow-up polynomial contrasts revealed a significant linear decrease over presentations consistent with a habituation interpretation [$F(1, 29) = 4.913$, $MSE = 0.268$, $P = 0.035$], but no significant higher order response patterns (P's > 0.05, for quadratic and cubic polynomials). There was also a main effect of valence [$F(2, 58) = 27.805$, $MSE = 0.24$, $P = 0.034 \times 10^{-7}$]. Greater activity was observed during negative images than neutral images [$F(1, 29) = 57.823$, $MSE = 0.45$, $P = 0.022 \times 10^{-6}$], during positive images than neutral images [$F(1, 29) = 19.021$, $MSE = 0.55$, $P = 0.014 \times 10^{-2}$] and also during negative than positive images [$F(1, 29) = 7.93$, $MSE = 0.436$, $P = 0.0087$]. Finally, an interaction revealed that the relationship between repetition and activity depended on valence [$F(5.21, 232) = 4.85$, $MSE = 0.336$, $P = 0.015 \times 10^{-3}$, Greenhouse–Geisser corrected]. The linear decrease over presentations was greater for negative than neutral valence [$F(1, 29) = 15.32$, $MSE = 0.346$, $P = 0.00051$], and for positive than neutral valence [$F(1, 29) = 4.33$, $MSE = 0.417$, $P = 0.046$]. As shown in Figure 2C, clusters in this group exhibited a pattern of responding strongly during the first presentation of positive images and first three presentations of negative images, and plateaued to levels similar to neutral images by the fifth presentation. Activity also plateaued to levels above the fixation baseline. Descriptively, Group 2 brain regions overlapped most with visual/occipital and dorsal attention networks (Figure 3).

Group 3: a non-linear response pattern with RP of affective and neutral stimuli

Group 3 included bilateral frontopolar cortex, right lateral posterior parietal cortex, and posterior cingulate cortex and precuneus (Figure 2E and F). Combining activity across clusters, a repeated-measures ANOVA revealed a main effect of repetition [$F(2.72, 116) = 8.94$, $MSE = 0.409$, $P = 0.03 \times 10^{-3}$, Greenhouse–Geisser corrected]. Follow-up polynomial contrasts revealed a significance quadratic effect over presentations [$F(1, 28) = 40.09$, $MSE = 0.086$, $P = 0.0075 \times 10^{-4}$], and a cubic effect [$F(1, 28) = 19.18$, $MSE = 0.074$, $P = 0.015 \times 10^{-2}$], but no linear effect ($P = 0.93$). There was also a main effect of affect category [$F(2, 56) = 7.38$, $MSE = 0.165$, $P = 0.0014$]. Greater activity was observed during positive images than neutral images [$F(1, 28) = 7.51$, $MSE = 0.363$, $P = 0.011$], and positive *vs* negative images [$F(1, 29) = 11.029$, $MSE = 0.397$, $P = 0.0025$], but not negative *vs* neutral images ($P = 0.36$). The repetition by affect category interaction was not significant ($P = 0.6$). As shown in Figure 2E, activity in this group showed no response on the first presentation, a large increase in response during the second presentation or first RP and then a gradual diminishing to no difference from fixation by the fifth presentation. This pattern occurred regardless of affect category. To assess whether the lack of responding on the first trial was incidentally due to a poor fit with the canonical hemodynamic response function (e.g. a significantly delayed response), we extracted and plotted time courses (Supplementary Figure S3). Although the time courses should be interpreted with reservation given the rapid event-related design, the time course for Group 3 is consistent with the ANOVA; there was no response on the first trial followed by a larger response on the second trial, and so forth. Descriptively, Group 3 brain regions overlapped with default mode and frontoparietal networks (Figure 3).

Brain regions responsive during repetition across stimuli of the same affect category

Patterns of diminishing activity observed using the aforementioned analyses may reflect 'affective adaptation', in which the accumulation of affective responses leads to neuronal fatigue (i.e. by analogy to sensory adaptation) rather than habituation. Although habituation is considered to be more stimulus specific so as to ascertain the value of particular stimuli for behavior (and not overgeneralizing to similar but novel stimuli for which the value is unknown), adaptation is considered to generalize across stimuli (Rankin *et al*., 2009). To address this, we examined whether a diminishing response pattern occurs across distinct images that share an affect category (see Methods). Contrary to an affective adaptation account, we found that no brain regions surpassed significance at the corrected threshold. Removing the cluster threshold, but keeping the voxel-level threshold ($P < 0.001$, uncorrected), revealed a small cluster in the anterior, dorsomedial prefrontal cortex (MNI = [6, 45, 36], and [−6, 54, 21]), tentatively suggesting the possibility that this area may be involved in stimulus generalization. But overall, these findings suggest that RP-related findings are unlikely to be due to affective adaptation in our task paradigm. In contrast, we did find evidence for the inverse, or a 'sensitization' pattern in the occipital cortex and adjacent temporal and parietal areas, resembling the topography of Group 2 (Supplementary Figure S5).

Table 2. Summary of activation clusters, group affiliations and ANOVA results

Group	Area	X	Y	Z	A η2	P η2	A × P η2	A	P	A × P	Silh.
1	Inferior frontal gyrus	33	36	−15	0.12	0.22	0.05	+	++++		0.52
1	Inferior frontal gyrus	−27	33	−6	0.18	0.20	0.05	++	++++		0.44
1	Inferior frontal gyrus	−33	33	−15	0.40	0.16	0.06	++++	+++		0.24
1	Inferior frontal gyrus	−51	30	9	0.04	0.19	0.03		++++		0.40
1	Inferior frontal gyrus	−51	27	−3	0.03	0.18	0.04		+++		0.56
1	Inferior frontal gyrus	57	12	21	0.09	0.23	0.03		++++		0.37
1	Medial frontal gyrus	−3	57	21	0.03	0.16	0.08		+++	++	0.53
1	Middle frontal gyrus	−36	30	15	0.06	0.20	0.03		++++		0.44
1	Superior frontal gyrus	−9	54	33	0.01	0.20	0.05		++++		0.51
1	Postcentral gyrus	66	−15	24	0.04	0.22	0.06		++++		0.37
1	Precentral gyrus	−42	3	27	0.25	0.20	0.05	+++	++++		0.05
1	Inferior parietal lobule	−60	−21	27	0.13	0.17	0.05	+	+++		0.34
1	Inferior parietal lobule	−48	−27	45	0.05	0.20	0.07		++++	+	0.28
1	Inferior parietal lobule	−60	−27	36	0.17	0.17	0.05	++	+++		0.09
1	Inferior parietal lobule	−33	−39	48	0.10	0.18	0.06	+	+++		0.07
1	Inferior temporal gyrus	63	−57	−12	0.06	0.20	0.00		++++		0.13
1	Middle temporal gyrus	−39	−57	6	0.02	0.22	0.04		++++		0.56
1	Temporal lobe	−42	−6	−15	0.29	0.17	0.02	++++	+++		0.08
1	Fusiform gyrus	45	−45	−21	0.12	0.20	0.04	+	++++		0.35
1	Lingual gyrus	15	−48	−3	0.30	0.11	0.07	++++	++	+	0.20
1	Lingual gyrus	−18	−54	3	0.25	0.14	0.06	+++	++		0.18
1	Middle occipital gyrus	48	−72	0	0.24	0.14	0.14	+++	++	++++	−0.09
1	Amygdala	24	−6	−18	0.24	0.22	0.02	+++	++++		0.38
1	Amygdala	−18	−6	−15	0.43	0.16	0.06	++++	+++		0.00
1	Caudate	−21	6	27	0.08	0.23	0.03		++++		0.41
1	Caudate	−6	12	9	0.05	0.25	0.04		++++		0.58
1	Caudate	3	6	9	0.04	0.22	0.03		++++		0.50
1	Caudate	−12	−12	18	0.00	0.23	0.04		++++		0.42
1	Claustrum	−36	−18	−15	0.08	0.21	0.04		++++		0.53
1	Dorsal striatum	−18	3	12	0.03	0.17	0.04		+++		0.57
1	Parahippocampal gyrus	−30	−6	−24	0.14	0.25	0.06	+	++++		0.57
1	Parahippocampal gyrus	−24	−21	−24	0.06	0.23	0.03		++++		0.51
1	Parahippocampal gyrus	−21	−21	−15	0.10	0.22	0.03	+	++++		0.47
1	Parahippocampal gyrus	−18	−36	−12	0.11	0.20	0.04	+	++++		0.28
1	Parahippocampal gyrus	15	−39	−9	0.19	0.18	0.05	++	+++		0.19
1	Parahippocampal gyrus	−42	−45	−3	0.04	0.29	0.03		++++		0.49
1	Cerebellum	−3	−51	−42	0.12	0.22	0.07	+	++++	+	0.27
1	Cerebellum	21	−78	−54	0.03	0.17	0.04		+++		0.49
2	Inferior frontal gyrus	42	6	21	0.25	0.11	0.05	+++	++		0.30
2	Cuneus	12	−87	6	0.46	0.08	0.15	++++		++++	0.48
2	Precuneus	27	−69	39	0.30	0.13	0.07	++++	++	+	0.64
2	Precuneus	−27	−72	27	0.42	0.08	0.12	++++		+++	0.73
2	Superior parietal lobule	−30	−51	51	0.12	0.08	0.05	+	+		0.47
2	Superior parietal lobule	27	−57	48	0.41	0.10	0.07	++++	+	+	0.63
2	Superior parietal lobule	−21	−66	48	0.39	0.08	0.09	++++		++	0.71
2	Inferior temporal gyrus	−42	−69	−6	0.39	0.17	0.11	++++	+++	+++	0.49
2	Middle temporal gyrus	45	−60	−9	0.43	0.13	0.08	++++	++	+	0.60
2	Fusiform gyrus	30	−48	−18	0.35	0.21	0.16	++++	++++	++++	0.37
2	Fusiform gyrus	30	−63	−9	0.55	0.12	0.18	++++	++	++++	0.76
2	Fusiform gyrus	−27	−66	−15	0.52	0.15	0.14	++++	+++	++++	0.63
2	Lingual gyrus	−24	−78	−9	0.49	0.05	0.15	++++		++++	0.77
2	Lingual gyrus	15	−78	−6	0.47	0.10	0.15	++++	+	++++	0.75
2	Lingual gyrus	−12	−81	−9	0.42	0.08	0.12	++++		+++	0.64
2	Lingual gyrus	−9	−90	0	0.50	0.06	0.16	++++		++++	0.44
2	Middle occipital gyrus	36	−81	9	0.52	0.09	0.23	++++	+	++++	0.70
2	Middle occipital gyrus	−30	−87	9	0.58	0.09	0.26	++++	+	++++	0.73
3	Middle frontal gyrus	30	57	3	0.30	0.22	0.02	++++	++++		0.81
3	Middle frontal gyrus	30	57	21	0.08	0.20	0.03		++++		0.73
3	Middle frontal gyrus	−36	51	6	0.14	0.18	0.02	+	++++		0.77
3	Middle frontal gyrus	51	18	42	0.08	0.17	0.05		+++		0.76
3	Cingulate gyrus	3	−33	39	0.18	0.19	0.04	++	++++		0.77
3	Posterior cingulate	3	−30	21	0.18	0.18	0.05	++	++++		0.76

(continued)

Table 2. (continued)

Group	Area	X	Y	Z	A η2	P η2	A × P η2	A	P	A × P	Silh.
3	Cuneus	−6	−75	30	0.41	0.04	0.05	++++			0.53
3	Inferior parietal lobule	57	−36	48	0.02	0.17	0.07		+++	+	0.72
3	Inferior parietal lobule	42	−57	54	0.02	0.21	0.03		++++		0.79
3	Precuneus	15	−51	36	0.31	0.18	0.04	++++	+++		0.76
3	Precuneus	−12	−60	66	0.18	0.19	0.02	++	++++		−0.04
3	Precuneus	9	−66	60	0.18	0.21	0.02	++	++++		0.53
3	Precuneus	6	−69	39	0.37	0.20	0.03	++++	++++		0.81
3	Precuneus	−6	−69	54	0.27	0.19	0.02	++++	++++		0.19
3	Angular gyrus	45	−60	42	0.35	0.18	0.04	++++	+++		0.77
3	Supramarginal gyrus	54	−33	36	0.01	0.20	0.02		++++		0.31
3	Supramarginal gyrus	54	−45	42	0.23	0.18	0.08	+++	++++	++	0.79

Notes. Peak MNI coordinates are presented for significant regions observed in a repeated-measures ANOVA with 'A'ffect category and 'P'resentation as factors ($P < 0.05$, FWE-corrected). Regions are organized into three groups based on similarity of response patterns *k*-means clustering analysis. Significance for follow-up main effects and interactions are indicated as follows: $^{++++}P < 0.0001$; $^{+++}P < 0.001$; $^{++}P < 0.01$; $^{+}P < 0.05$. Effect sizes ($\eta 2$) are provided for relative comparisons across factors but must be interpreted with caution since identification of voxels in clusters was not independent of magnitude of effects. Silhouette values are also provided to assess how well the cluster is reflected by the group.

Discussion

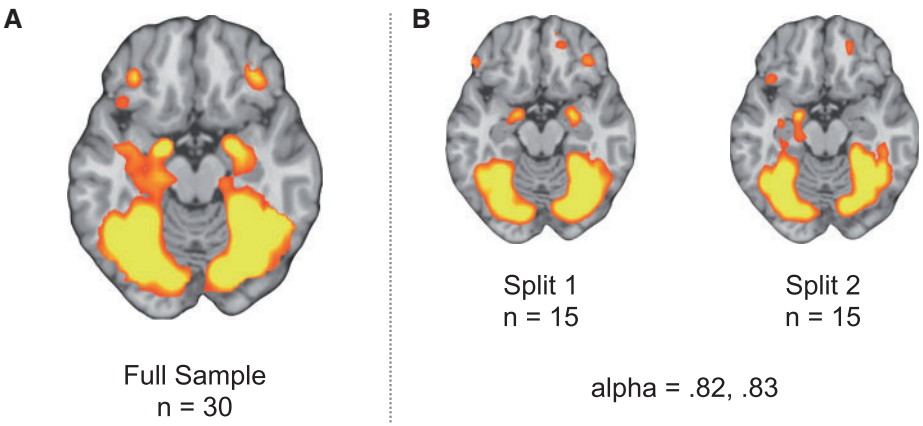
Our study makes three contributions to the study of RP using human neuroimaging. First, we found that different response patterns occur with RP. For Groups 1 and 2, monotonically diminishing activity occurred with RP, albeit in different ways for each group depending on the affect category of the stimulus and the extent to which responses plateaued to levels above baseline. For Group 3, we observed a novel, non-monotonic response pattern. Second, we found that a much larger set of brain regions were responsive during RP than has been implicated in prior neuroimaging studies. As discussed below, many of these brain regions may have been overlooked by prior studies depending on which portions of the response pattern they sampled from in their analyses. And third, we provide a first look at how RP relates with the functional connectome by spatial overlap of canonical intrinsic network maps with the activation groups observed in our study. Taken together, our findings suggest that neural activity during RP involves several heterogeneous dynamic response profiles in spatially distributed areas, portions of which may be usefully organized by the topology of intrinsic networks.

We observed these findings by using a data-driven, clustering analysis (e.g. Gonzalez-Castillo *et al.*, 2012; Neta *et al.*, 2015). As a data-reduction technique, clustering algorithms have the advantage of simplifying the results by identifying common patterns that recur across activation clusters instead of examining each activation cluster one by one. By design, some activation clusters may not fit their group assignments as well as others. Therefore, we make the caveat that conclusions involving the specific group response patterns extend only to the activation clusters that well-resemble the group pattern. Findings for specific activation clusters and how well they fit their group assignments (e.g. on the basis of Silhouette values) are available in the Supplementary Material. Our conclusions below rest mainly on the overarching finding that RP involves at least three (or perhaps more) different response patterns.

For Group 1, which included the amygdala and the hippocampus, activity diminished monotonically and by the fifth stimulus presentation was not different from the fixation baseline. This response was most consistent with a habituation-like response profile. In comparison, Group 2, which consisted of activity in the occipital lobe and adjacent areas, also showed monotonically diminishing responses but only for affectively arousing stimuli and responses plateaued to levels above the fixation baseline. Several prior studies have shown greater activity in primary visual cortex and fusiform cortical areas for affective visual stimuli (Lang *et al.*, 1998; Vuilleumier *et al.*, 2001; Pessoa *et al.*, 2006; Satpute *et al.*, 2015a), an effect that depends on reentrant connections from the amygdala (Vuilleumier *et al.*, 2004). Our results are more consistent with a reentrant signaling mechanism than sensory adaptation or habituation (also see, Haenny and Schiller, 1987); repeated neutral stimuli did not show diminishing activity across trials, as would have been expected by the latter accounts but not by reentrant signaling for arousing visual stimuli.

We also observed a pattern of sensitization across different stimuli of the same affect category in the occipital and adjacent areas. Such sensitization is expected from a predictive coding standpoint. That is, a reasonable expectation of visual perception is spatiotemporal continuity (Rao and Ballard, 1999). In our experiment however (like many others), spatiotemporal continuity is violated with the randomly ordered and temporally discretized presentation of natural scene images. As such, the sensitization pattern may reflect prediction error signals, which accumulate over trials. That is, if spatiotemporal contiguity is the typical expectation, this is violated to greater degrees with repeated presentation of different spatiotemporal stimuli. The sensitization across different images also diminished across sets of trial presentations (i.e. from novel presentations, to the fifth repetition, etc.), consistent with the notion that prediction error decreased as all stimuli became more familiar. Notably, from a predictive coding standpoint, these findings may suggest that activity in the visual cortex sends forward prediction error signals not only for spatiotemporal visual properties (Rao and Ballard, 1999; Alink *et al.* 2010), but also for affective properties insofar as there was greater activity in early visual cortex during affective stimuli that rapidly habituated to levels similar to activity during neutral images (Figure 2C and D). These findings are also consistent with degeneracy (Edelman and Gally, 2001) of affective experience, in which affective experiences are constructed by a distributed architecture that also involves early sensory brain regions (Satpute *et al.*, 2015a).

Group 3 showed a remarkably distinct response profile than those from Group 1 or Group 2. There was little to no response on the first (novel) presentation followed by a heightened response on first repetition that subsequently diminished with



C

	Neutral					Negative					Positive				
Area	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Occipital [-30, -87, 9]	-1.31	-0.52	-0.81	-0.94	-0.66	1.23	1.76	1.87	0.09	-0.51	1.02	-0.62	-0.26	-0.40	0.06
Occipital [36, -81, 9]	-1.08	-0.46	-0.84	-1.00	-0.71	1.37	1.70	1.83	-0.06	-0.58	1.11	-0.63	-0.53	-0.16	0.04
Lingual [-9, -90, 0]	-1.75	-0.35	-0.76	-1.23	-0.79	0.49	0.43	0.69	-0.61	-0.35	2.43	0.59	0.40	0.37	0.42
...															

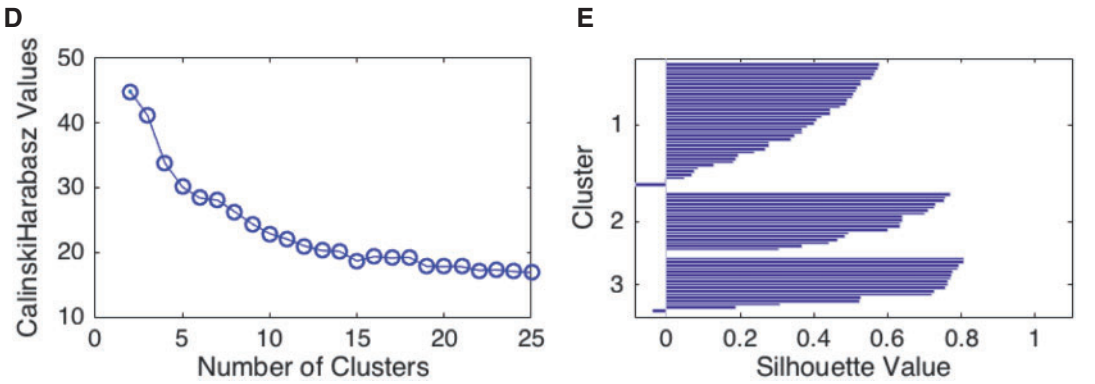


Fig. 1. Data analysis steps. (A) Upon calculating first-level models, an omnibus *F*-test was used to identify activation clusters that were sensitive to the task conditions, but does not stipulate the precise arrangement of the condition differences. (B) Reliability of the *F*-test was calculated in two orthogonal split-halves samples by correlating the *F*-values for voxels calculated in one sample with *F*-values for voxels calculated in another sample. (C) Parameter estimates for each condition were averaged across voxels and subjects for each activation cluster, and *z*-scored across the 15 conditions. A portion of the table for three clusters is shown for illustration. (D) Data reduction using *k*-means clusters was performed. A stopping rule of three was selected based on an elbow criterion using Calinksi–Harabasz values. (E) Silhouette values illustrate the degree to which activation clusters resembled group assignments. Although many activation clusters have acceptable Silhouette values for the group (particularly for Groups 2 and 3), some activation clusters are not well represented by the group they were assigned to. Analysis focused on groups, and thus pertain more for activation clusters that better resemble the group profile. Plots of individual activation clusters (in order of Calinski Harabasz values) are also provided in the Supplementary Material for a more detailed examination. The cluster analysis was also performed on split-halves samples presented in the Supplementary Material.

additional repetitions. This response pattern was observed in several activation clusters, across all three affect categories, and reliably across split-halves samples. This profile is also unlikely to be due to a delayed hemodynamic response for the first trial, based on time-course plots. It remains possible that this response profile (and also those above) is particular to the study design we used: a rapid event-related design with intermixed, affective and neutral visual stimuli. Replication using different study designs such as a single trial design or by presenting stimuli from different sensory modalities would be important to assess its generalizability.

Speculatively, the functional significance of the response pattern for Group 3 may reflect engaging in a mnemonic strategy for task completion. Participants were instructed to make arousal judgments. For novel stimuli, these arousal judgments may be driven by perceptual, semantic or interoceptive information, but cannot rely on prior exposures of the stimulus. The first repetition, however, provides an opportunity to use memory to facilitate these judgments. Memory of the prior presentation may be used to more rapidly process any aspect of the current presentation—be it the visual processing of the image, imbuing the image with meaning, generating visceral responses to the image, or perhaps generating a simulated affective response to the image as a shortcut rather going through a full-blown affective response. Accordingly, activity in these brain regions may reflect mnemonic processes potentially relating to episodic memory (Cabeza *et al.*, 2002; Svoboda *et al.*, 2006), semantic memory (Binder *et al.*, 2009), pattern completion

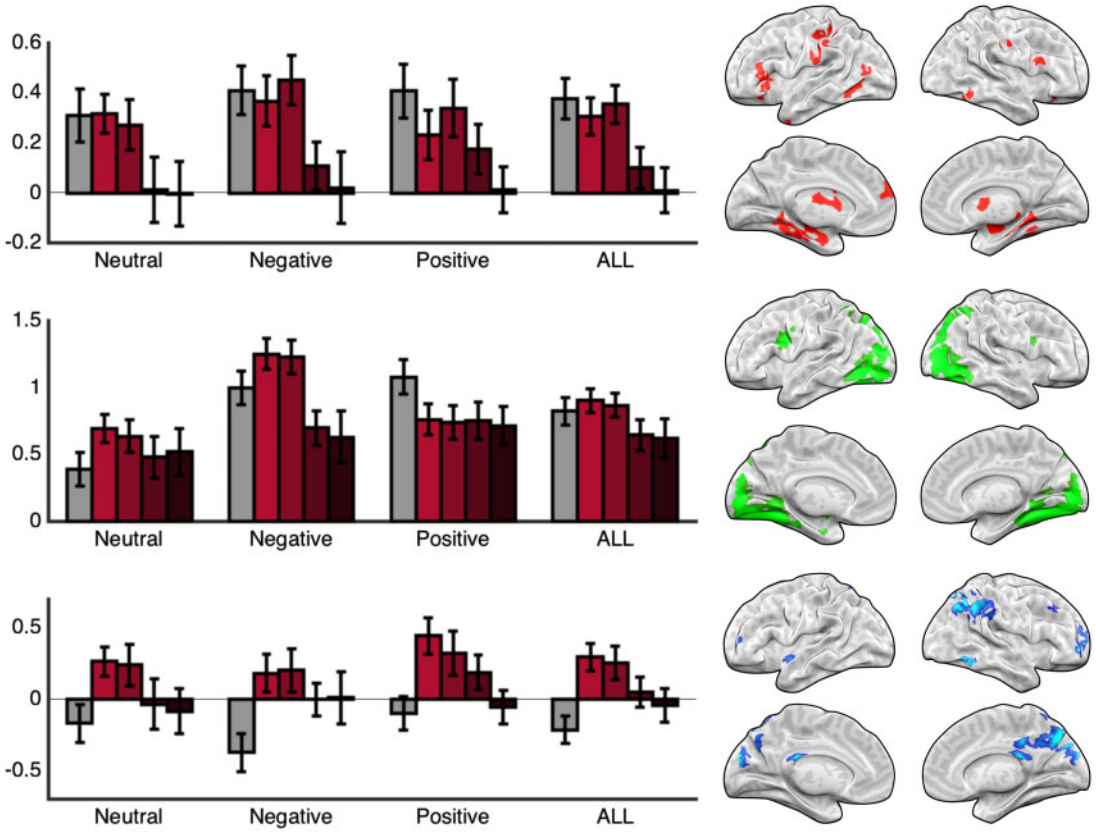


Fig. 2. Response profiles occurring with RP for each group, separated by valence. Mean percent signal change for the first (novel) image presentation is depicted by the grey bars, and for the second through fifth (repetition) presentations are depicted in shades of red from bright to dark. The top row (A and B) is for Group 1, and shows diminishing activity across trials. The middle row (C and D) is for Group 2, and shows a response profile of greater activity on early trials for affective images relative to neutral images. The bottom row (E and F) is for Group 3, and shows a unique response pattern with no response for the novel presentation, a heightened response on the first repetition, followed by diminishing activity. L, left; R, right.

(Hunsaker and Kesner, 2013) or simulation (Barsalou, 2008). In each case, these mnemonic processes would likely come into play on the first repetition in which retrieval of the image is both possible (unlike on the first novel presentation), and also become less demanding with successive repetitions, which follows the response pattern for Group 3. While speculative, our account suggests that self-reported arousal may be computed in different ways, relying more on 'bottom up' *vs* 'top-down' sources of information depending in part on whether a stimulus is novel or familiar, respectively.

Implications for the neuroscience of repeated presentation

RP is used to study a wide array of phenomena across disciplines in psychology and neuroscience. Prior neuroimaging studies on RP have constrained their search for the neural correlates of RP both spatially, by rarely focusing on brain regions outside the amygdala, the hippocampus, and a few of cortical areas, and temporally, by focusing on monotonically decreasing activity with RP (Breiter *et al.*, 1996; Whalen *et al.*, 1998; Becerra *et al.*, 1999; Poellinger *et al.*, 2001; Pfleiderer *et al.*, 2002; Phan *et al.*, 2003; Ishai *et al.*, 2004; Somerville *et al.*, 2004; Yamaguchi *et al.*, 2004; Johnstone *et al.*, 2005; Hooker *et al.*, 2006; McNally, 2007; Kleinhans *et al.*, 2009; Mutschler *et al.*, 2010; Moriguchi *et al.*, 2011; Blackford *et al.*, 2012). These constraints are well-motivated by prior work in non-human animals and are important for translating research in non-human to human neuroscience (Breiter *et al.*, 1996; Whalen *et al.*, 1998; Vinogradova, 2001; Kumaran and Maguire, 2009; Murty *et al.*, 2013). Yet, other lines of work in non-human animals suggest that the neuroscience of RP involves a wider array of brain regions with a more complex response patterns. For instance, multiple neurotransmitter systems play a role in behavioral habituation (Leussis and Bolivar, 2006), and neural activity important for behavioral habituation need not mirror the behavioral response profile of habituation (Vinogradova, 2001). Using a more flexible, data-driven approach, our study builds upon these ideas by uncovering several additional brain regions with different response profiles that respond during RP.

Our findings have implications for several research areas that have used RP to study a variety of phenomena. Research on novelty processing and the orienting response often compares novel stimuli with stimuli that have been well-familiarized (e.g. Opitz *et al.*, 1999; Dobbins and Wagner, 2005; Moriguchi *et al.*, 2011). This comparison samples from the ends of the response profiles. It would therefore identify activation clusters that resemble the profile of Group 1, and clusters in Group 2 to the extent that the novel stimuli are also affectively arousing, but likely fail to observe activity in clusters that show profiles resembling Group 3. fMRI research on habituation typically searches for brain regions that show habituation-like response profiles, and thus would not implicate brain regions that resemble the activation pattern of Group 3. Similar considerations

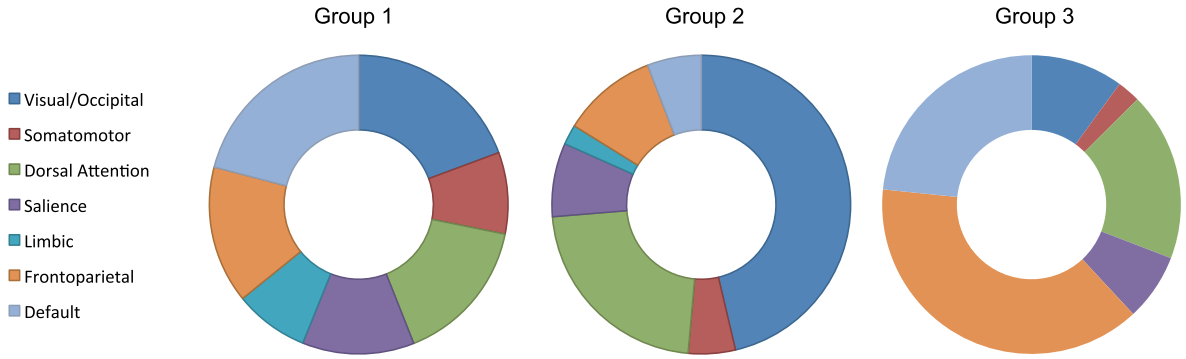


Fig. 3. Overlap between brain regions sharing response profiles and resting-state functional networks. (A) Activations in Group 1 fall in several networks including the default mode, frontoparietal, dorsal attention and salience networks. (B) Activations in Group 2 fall primarily in visual/occipital and dorsal attention networks. (C) Activations in Group 3 fall primarily in default mode and frontoparietal networks.

may pertain to research on repetition priming and the inferential methodology of 'repetition suppression' (e.g. Dehaene *et al.*, 2001; Henson and Rugg, 2003; Gold *et al.*, 2006; Grill-Spector *et al.*, 2006). Relevant studies often search for brain regions showing reduced activity across two successive presentations of stimuli as evidence that corresponding brain regions are involved in processes engaged by both stimuli. Our findings suggest that observing these patterns depends on what portion of the response pattern is being sample from, which may depend for instance on the extent to which the stimuli were already familiarized beforehand. For instance, a repetition suppression analysis of our study may reveal activity in Group 1 if comparing novel trials with the first repeated presentation, or Group 3 if comparing the first and second repeated presentations for the analysis (i.e. in cases for which participants are initially presented with all stimuli once so as to familiarize them beforehand).

Implications for affective neuroscience

Affective experience is considered to vary along valence and arousal dimensions (Wundt, 1913; Russell, 1980; Barrett, 2004; Kuppens *et al.*, 2013). Prior neuroimaging work has used both univariate and multivariate methods to examine which brain regions are associated with these dimensions. Using univariate approaches, numerous fMRI studies have observed differences in activity when comparing pleasant and unpleasant stimuli in various brain regions (Canli *et al.*, 1998; Anderson *et al.*, 2003; Anders *et al.*, 2004; Lewis *et al.*, 2007), suggesting initially that valence may involve distinct gross neuroanatomical circuits (e.g. a 'pleasure center' of the brain). However, meta-analytic summaries have failed to find effects that are consistent across them (Hayes *et al.*, 2014; Lindquist *et al.*, 2016), suggesting that the brain regions found in one study corresponding with valence are not necessarily the same as those found in another study. Our study is limited in that the negative images were rated as more arousing than the positive images, but it may nonetheless provide insight on how the brain represents affect. At first glance, our findings may be considered to support differentiation of valence and arousal. Similar to many previous studies, we used a univariate approach to identify which brain regions respond more strongly during presentation of affect-inducing images. Groups 1 and 2 showed the greatest activity during highly arousing unpleasant images, followed by the mid-arousing pleasant images, and least for the low arousing neutral images—suggesting that they track with arousal. Group 3 showed more activity during the mid-arousing pleasant images than negative and neutral images, suggesting that they track with valence. But the examination of repeated presentation suggests otherwise (also see Ishai *et al.*, 2004). Brain regions that are selective for a particular affect category would be expected to show modulation with RP for that category but not others. However, all three groups in our study showed diminishing response patterns for both unpleasant and pleasant stimuli. Our findings demonstrate that when valence-related differences in neural activity are observed, this does not necessarily indicate valence specificity.

Our findings also relate to the neuroscience of emotion regulation. Many of the brain regions we found to be associated with the 'passive' learning of habituation overlap with those observed in prior studies of 'active' forms of emotion regulation, such as reappraisal (in which individuals are instructed to reinterpret the meaning of a stimulus so as to reduce its affective impact). Like our findings, prior studies on reappraisal have also observed activity in the frontoparietal network, including the ventrolateral prefrontal cortex, lateral middle frontal gyrus and lateral intraparietal area (Buhle *et al.*, 2013). Such overlap suggests several possibilities for further exploration. For instance, habituation is typically characterized as 'passive learning' because it does not require reinforcement or punishment, but on a neural level, more active learning and memory strategies may nonetheless underlie behavior (McNally *et al.*, 2011; Li and McNally, 2014). As such, these groups of brain regions may serve as ROIs for future work ranging from examining the basic mechanisms for processing repeated stimulus presentations to identifying biomarkers for outcome success variables in exposure therapy.

Limitations

Our study has three main limitations that may be addressed in future work. First, we were unable to examine activity in the medial orbitofrontal cortex which has been much of the focus for valence (Öngür and Price, 2000; Grabenhorst and Rolls, 2011; Chikazoe *et al.*, 2014; Lindquist *et al.*, 2016). Second, valence may be organized on a finer spatial resolution than we were capable of examining in this study perhaps involving brain stem nuclei (Satpute *et al.*, 2013). Finally, there were only a handful of stimuli per affect category, which may increase the potential influence of confounding stimulus dimensions (e.g. visual complexity, social content, etc.). These stimulus issues limit

interpretations of findings showing differences related to affect category, albeit are of less concern for the main effect of repetition. To mitigate this, the selected images for pleasant and unpleasant affect categories were matched beforehand for normative valence, and images in all three affect categories were selected for approximately similar degrees of social information (see Methods).

Conclusions and future directions

RP has been used in a wide variety of situations including the study of novelty, repetition priming, habituation, and the clinical implementation of habituation, or exposure therapy (Abramowitz *et al*., 2011). Although prior neuroimaging work has largely focused on neural response patterns that in loosely resemble behavioral habituation, research in non-human animals suggests that this need not be the case. Our study identified novel response patterns and a wider set of affiliated brain regions that may be of importance during RP. In so doing, the present findings take important steps toward a whole-brain understanding of phenomena related to RP. Nevertheless, there remains a considerable gap between the focus of our study, which is on how RP relates to diverse hemodynamic response patterns, and making clear the neural mechanisms that link RP to behavioral or experiential outcomes, like habituation (Rankin *et al*., 2009).

One avenue for future work is to examine how the hemodynamic response profiles we observed relate to direct measures of neural activity. Previous neuroimaging studies have shown habituation-like response patterns in brain regions known to have neurons that also habituate on the basis of cell-recording studies, but rarely are hemodynamic and neural measures recorded at once. In one study to do so, Obrig *et al*. (2002) found a close coupling between simultaneous measurements of visually evoked potentials and hemodynamic responses with RP of visual stimuli, but caution against assuming that such coupling is pervasive throughout the brain. Hence, whether the non-monotonic hemodynamic response pattern we observed also relates with neural activity would be an important consideration for future work. Indeed, hemodynamic responses are known to stem from heterogeneous sources of neural activity, albeit most strongly relate to the accumulation of pre-synaptic potentials (Huettel *et al*., 2004). Still, Vinogradova (2001) described several different neural response patterns occurring with RP based on cell recording studies of the hippocampus and hippocampal inputs. Some neurons rapidly habituated to baseline firing rates, others plateaued to levels above baseline, and still others showed diminished responses on the first presentation followed by a gradual return to baseline. Our work suggests that these response profiles and potentially others are also present in many other parts of the brain, which may be tested in future work.

Another direction for future work is to understand how the response profiles we identified in this study relate to behavioral responses to habituation. Our study provides a limited opportunity to examine how the neural response profiles relate to behavioral self-report ratings on a subject-by-subject or trial-by-trial level. Similarly, the average reaction times, which diminished over time, also resembled diminishing activity in these groups. Using a more graded response scale or other behavioral tests of habituation (e.g. spontaneous recovery) would be of interest to explore the link between response profiles and behavior more directly. Uncovering precisely what functional contribution each of these groups makes may be addressed by manipulating component processes underlying affective experience (Satpute *et al*., 2012), including additional relevant measures (e.g. physiological response profiles, memory), and implementing computational learning models that may account for differential response patterns (e.g. predictive coding models, Friston, 2005; Hunsaker and Kesner, 2013).

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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