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A unique role for the human amygdala in novelty detection

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ABSTRACT

Previous research indicates that the amygdala and hippocampus are sensitive to novelty; however, two types of novelty can be distinguished – stimuli that are ordinary, but novel in the current context, and stimuli that are unusual. Using functional magnetic resonance imaging, we examined blood oxygen dependent level (BOLD) response of the human amygdala and hippocampus to novel, commonly seen objects versus novel unusual objects. When presented with the novel common stimuli, the BOLD signal increased significantly in both the amygdala and hippocampus. However, for the novel unusual stimuli, only the amygdala showed an increased response compared to the novel common stimuli. These findings suggest that the amygdala is distinctly responsive to novel unusual stimuli, making a unique contribution to the novelty detection circuit.

Introduction

Humans must continually process vast amounts of incoming sensory information, requiring the brain to efficiently determine which stimuli require attention or memory encoding. Given limited resources, the ability to detect and direct attention to novel stimuli has substantial adaptive value. Novelty detection is supported by a coordinated network of brain regions in the medial temporal lobe, visual, parietal and prefrontal cortices, and the dopamine midbrain (Hughes, 2007; Kiehl et al., 2001; Ranganath and Rainer, 2003; Squire et al., 2004). Of these brain regions, the medial temporal lobe has received substantial attention. Converging support for medial temporal lobe involvement in novelty detection comes from single-cell recording (Fried et al., 1997; Rutishauser et al., 2006), lesion (Knight, 1996; Stark and Squire, 2003), and functional neuroimaging (Gonsalves et al., 2005; Kirwan et al., 2009) studies.

Within the medial temporal lobe, the hippocampus has long been recognized as an important brain structure for the detection of and subsequent memory for novel events (Knight, 1996; Kumaran and Maguire, 2009; Ranganath and Rainer, 2003). This function is usually interpreted within the context of the hippocampus's pivotal role in declarative memory, as the recognition of a new stimulus depends upon the ability to contrast it with stored memories (Hughes, 2007), and because new stimuli particularly warrant encoding.

Anterior to the hippocampus, the amygdala has also been identified as part of a neural novelty detection circuit (Kiehl et al., 2005). Recent studies indicate that the amygdala responds to novel stimuli, such as novel human faces (Schwartz et al., 2003; Wright et al., 2003) or novel sounds (Kiehl et al., 2005). The exact function of this response is uncertain, but it may be interpreted within the context of the amygdala's critical role in evaluating the emotional significance (Breiter et al., 1996; Whalen et al., 1998), arousal (Kensinger and Schacter, 2006; Lewis et al., 2007), or salience (Ewbank et al., 2009) of stimuli (for a review, see Zald, 2003). In animal studies, the amygdala response to novelty appears critical in mediating neophobic responses (Hughes, 2007), consistent with the amygdala's role in fear and avoidance behaviors (Davis and Whalen, 2001) .

While it is clear that novel stimuli engage both the amygdala and hippocampus, it is unclear whether novelty responses in the hippocampus and amygdala reflect a common underlying process since the type of novel stimulus used often differs across studies. For instance, in studies of memory, a novel stimulus is typically defined as a stimulus not previously presented in the study (e.g., Tulving et al., 1996). These stimuli (such as a picture of a house, landscape or person) are not conceptually novel, or unusual—indeed the person may have experienced the particular type of stimulus many times before. Rather, the stimuli are only novel to the current context. In contrast, in research on motivation and emotion, a novel stimulus is often categorically unique and represents an object or situation with which the person has no previous experience (Hamann et al., 2002), for example, a leafy sea dragon or rendering of a futuristic skyscraper. Detection of these two types of novelty may have different functional consequences: detection of novel common stimuli may increase

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awareness of the stimulus in the current context, and detection of novel uncommon stimuli may allocate processing resources to determine what the stimulus is and whether it will have a positive or negative impact on the individual.

Prior studies have experimentally manipulated type of novelty to examine functional differences within the hippocampus (Strange et al., 1999) and between the hippocampus and parahippocampal cortex (Duzel et al., 2003; Pihlajamaki et al., 2004). To our knowledge, no neuroimaging studies have contrasted contextual and categorical novelty nor compared the novelty responses of the amygdala and hippocampus.

To examine the role of the amygdala and hippocampus in detecting different types of novelty, we used functional magnetic resonance imaging (fMRI) to measure the blood oxygen level dependent (BOLD) response to three types of stimuli—familiar common, novel common, and novel uncommon—in 29 healthy adults. The novel common images represented contextual novelty because they had not been seen before in the context of this study and the novel uncommon stimuli represented categorical novelty because they were unusual and unlikely to have been seen before in real life. The results demonstrate that the amygdala and hippocampus have different response profiles to the two distinct types of novelty.

Materials and methods

Participants

Thirty-two healthy adults (19 females, 13 males) with an average age of 22 years (SD = 3.1) participated in the study. Participants were mainly right-handed (91%) and represented multiple ethnic groups: 71% Caucasian, 16% Asian, and 13% African-American. Data from three participants were later removed from analysis due to excessive motion during the scan (see fMRI data below) for an analytic sample size of 29 participants. The study was approved by the Vanderbilt Institutional Review Board. Following a description of the study, all participants gave written informed consent and were reimbursed for their time.

Method

Stimuli

The common stimuli, both familiar and novel, consisted of images commonly seen in real life (e.g., chair, clock, tree). For the common stimuli, we used images from the International Affective Picture Set (IAPS; Lang et al., 1999), a collection of images rated on valence (how pleasant or unpleasant the image is; 1 to 9 rating) and arousal (how calm or excited the image makes you feel; 1 to 9 rating). We selected 71 pictures based on neutral valence (range 4–6), low arousal (range 1–5), and absence of human faces, social scenes, or potentially threatening images (e.g., tornado, prison). Examples of these images include flowers, mushrooms, a coffee mug, an umbrella, and shoes. We supplemented the IAPS pictures with 43 other images of similar types found in the public domain. The additional images were validated as common and neutral in an independent study (see Supplementary Materials). We randomly selected six of the common images to create the familiar set and the remaining 108 images comprised the novel common stimuli.

For the novel uncommon pictures, we selected 108 images based on the following features: unusual and not commonly seen, neutral emotional content, and absence of human faces or social scenes. Examples included complex graphic art, visually distorted images, unusual buildings (e.g., Prague Dancing House, futuristic skyscraper), and unusual plants or animals (e.g., leafy sea dragon). The majority ($n = 95$) of the images were selected from the public domain. Ten of the images were IAPS pictures that had been digitally manipulated (e.g., Chrome, Craquelure, Stained Glass, Ocean Ripple, Shear) using Photoshop (Version 10.1, Adobe Systems Incorporated) to obscure the original content of the image and make the image appear unusual. The remaining three images came from the IAPS and were rated as neutral but moderately arousing. Overall, the novel uncommon images were rated as relatively uncommon, neutral, and slightly arousing (see Supplementary Materials).

In summary, both the novel common and novel uncommon images represented contextual novelty in that they had not been previously seen in the scanner. The novel common and novel uncommon pictures differed in whether they were images often seen in real life or were uncommon, unusual pictures unlikely to have been seen before. None of the stimuli in the study contained human faces or explicit emotional content, characteristics previously shown to activate the amygdala. All images were converted to a standard size (345×401 pixels) to remove potential effects due to differential impact on the visual field caused by different image sizes.

fMRI task

We used a within-subjects design to test for brain responses to the passive viewing of three types of pictures: familiar, novel common, and novel uncommon. Pictures were presented to participants in the scanner using Eprime software (Version 1.1, Psychology Software Tools, Pittsburgh, PA). The fMRI paradigm, adapted from Schwartz et al. (2003), consisted of a familiarization and a test phase. During the familiarization phase, we presented the six familiar images 16 times each for 500 ms with a 500 ms interstimulus interval for a total of 96 s.

In the test phase, we presented alternating blocks of familiar, novel common, and novel uncommon pictures. By using a block design, we controlled predictability (another aspect of novelty) because each picture class was presented for the same overall duration and with the same probability (1/3 familiar, 1/3 novel common, and 1/3 novel uncommon), in contrast to oddball paradigms where novel events are typically more infrequent. Each of the two 174 s sessions consisted of three sections of images, each preceded by a 4 s fixation. Within each section of images, there were three 18 s blocks each of the familiar, novel common, and novel uncommon pictures (e.g., fixation cross, novel common block, familiar block, novel uncommon block, fixation cross). All images were presented for 1 s with no interstimulus intervals. Block order was counterbalanced across the two runs and was the same for each participant. For the familiar blocks, each of the six familiarized images were randomly presented three times within each block. For the novel common and novel uncommon blocks, images were randomly selected and never repeated.

fMRI data

Anatomical and functional (EPI) images were collected on a 3-T Phillips Achieva magnet (Philips Healthcare, Inc., Best, The Netherlands). High resolution T1-weighted anatomical images were collected (256 mm FOV, 170 slices, 1 mm, 0 mm gap) for structural brain information. Functional EPI images were acquired using a sequence optimized for the amygdala: 2 s TR, 22 ms TE; 90° flip angle; 240 mm FOV; 3×3 mm in plane resolution using an 80×80 matrix (reconstructed to 128×128), and higher-order shimming to limit susceptibility artifacts. Each volume comprised 30 2.5 mm (.25 gap) axial oblique slices (titled 15° anterior higher than posterior relative to the intercommisural plane) providing complete anterior–posterior coverage and inferior–superior coverage from the bottom of the temporal lobe to the top of the most dorsal part of the cingulate gyrus. For each participant, functional images were visually inspected for artifacts and signal dropout prior to analysis to ensure appropriate coverage of the amygdala and hippocampus regions of interest.

MRI data were preprocessed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm5/) and Matlab (Version 7.1, The MathWorks, Inc., Natick, MA). Data were slice time-corrected, corrected for motion (aligned to the first slice), coregistered to the structural image, normalized into

standard stereotactic space (MNI T1 template), resampled to 3×3×3 mm voxels, and high-pass filtered (128 s). Data were smoothed with a 5-mm FWHM Gaussian kernel to account for individual differences in brain anatomy. Participants ($n=3$) with substantial motion (>3 mm) were removed from subsequent analysis.

We used SPM5 to model each participant's response to the three types of stimuli (familiar, novel common, novel uncommon) using a block design (Friston et al., 1994) with each of the stimulus types as regressors. Next, we created contrast images for each stimulus type versus baseline. Participant-level contrast images were used for both the region of interest and whole-brain analysis as described below.

Data analysis

Regions of interest

For our *a priori* regions of interest, we extracted average percent signal change values from the anatomically-defined amygdala and hippocampus ROIs (aal templates; WFU Pick Atlas Version 2.4; Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002) for each participant and stimulus type using MarsBar (Brett et al., 2002). We conducted a repeated measures analysis of variance to test for overall differences in percent signal change across the three stimulus types (familiar, novel common, novel uncommon) using SAS statistical software (Version 9.1, SAS Institute, Inc., Cary, NC) . Following significant omnibus differences, we used paired *t*-tests to test for significant differences between familiar versus novel common images and novel common versus novel uncommon images. Preliminary analyses including gender and ethnicity confirmed no significant effects of either variable. We used an alpha of .05 for all analysis.

Whole-brain analysis

We also conducted a whole-brain analysis in SPM5 to identify other regions sensitive to novelty. To examine effects of stimulus type at the group level, we performed a second-level (random effects) analysis using the *t*-contrast images from each level of our factor (stimulus types) in a repeated measures analysis of variance model. At the group level, we performed two contrasts: novel common>familiar and novel uncommon> ommon. To correct for multiple comparisons, we used cluster-based thresholds calculated by simulations of data with the volume and spatial resolution (full width half-maximum) of our functional data using the AlphaSim module of AFNI (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). For the whole-brain analysis, a combined voxel threshold of $p<.005$ and contiguous cluster extent of 17 voxels provided Type I error control at alpha = .05. For the a priori regions, a voxel threshold of $p<.01$ and contiguous cluster sizes of 4 (amygdala) and 7 (hippocampus) voxels provided Type I error control at alpha = .05. Significant regions are presented in the Results section but are only briefly discussed since they are not the main focus of this paper.

Results

Regions of interest: Amygdala and hippocampus

To examine the effect of contextual novelty on the amygdala and hippocampus, we compared BOLD responses between the familiar and novel images of common objects and scenes. In the amygdala, novel common images increased BOLD response by 50% in the left amygdala and 47% in the right amygdala (Figs. 1a and 2a). Consistent with the amygdala results, both left and right hippocampi showed an increased response (63% and 91%, respectively) to the novel common compared to the familiar images (Figs. 1b and 2b).

To determine whether the amygdala or hippocampus responds to unusual stimuli above and beyond their response to contextual novelty, we compared BOLD responses to the novel uncommon images relative to the novel common images. The novel uncommon images produced a significantly larger response than novel common images for both the left (17%) and right (22%) amygdala (Figs. 1a and 2a). In contrast, neither left nor right hippocampus showed a differential response to the novel uncommon images (0% and 1% change, respectively; see Figs. 1b and 2b).

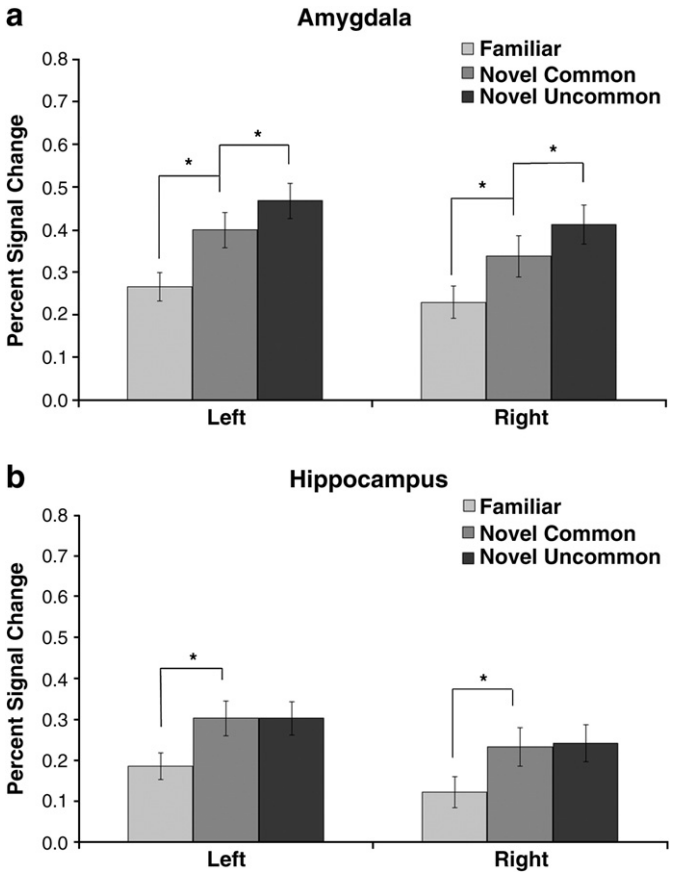

Fig. 1. Amygdala and hippocampus show different patterns of response to two types of novel stimuli. (a) In the amygdala, BOLD response increases parametrically to familiar, novel common and novel uncommon images. Response is greater for novel common relative to familiar images for both the left amygdala, $t(28)=4.49$, $p=.0001$, and right amygdala, $t(28)=4.04$, $p=.0004$. Amygdala response is also increased for novel uncommon images compared to novel common for both left, $t(28)=2.14$, $p=.04$, and right, $t(28)=2.49$, $p=.02$, hemispheres. (b) Left and right hippocampi show increased responses to novel common relative to familiar pictures ($t(28)=6.21$, $p=.0004$ and $t(28)=6.66$, $p=.0001$, respectively) but do not respond differentially to the two types of novel pictures (both p values>.59; novel uncommon = novel common). Error bars indicate SEM.

The novel uncommon images were rated as somewhat more arousing than the novel common images (3.81 vs. 4.10 on a 1–7 scale). The intertwining of novelty and arousal is ecologically expected; novel images are inherently arousing and it is adaptive for an organism to be aroused by unusual, not previously seen stimuli. However, because highly arousing words and images have been previously shown to engage the amygdala (Kensinger and Schacter, 2006; Lewis et al., 2007), we performed post-hoc correlation analyses to assess the degree to which arousal differences contributed to the amygdala response to novelty (see Supplementary Materials). Although there was a small (10–15%) shared contribution of arousal and novelty, the majority of the effect of novelty on amygdala response was uniquely attributable to novelty.

To more specifically control for the potential contribution of arousal on amygdala and hippocampus response to novelty, we also performed an additional event-related analysis (see Supplementary Materials). After controlling for image-specific arousal ratings, the main study findings held, providing evidence that the increased amygdala response to novel uncommon images was the result of

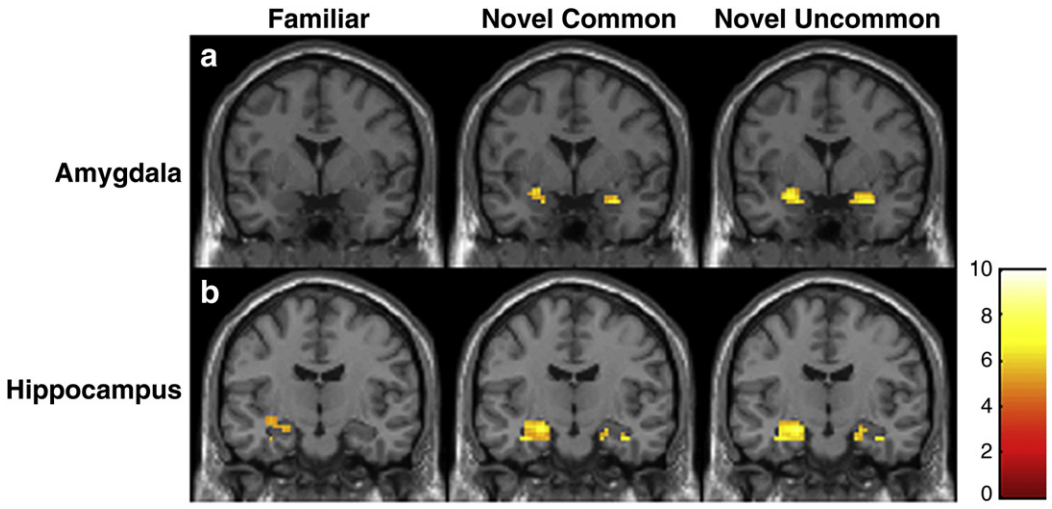

Fig. 2. Brain response to the three different picture types (versus baseline fixation cross). Activation maps are superimposed on a coronal section of a single standard (MNI canonical T1 image) brain image. Spread and degree of BOLD response can be seen for the (a) amygdala ($y=0$) and (b) hippocampus ($y=-12$). Activation maps are thresholded at $t=5$ to illustrate differences in spread and degree across conditions. The color bar represents t values (restricted to maximum $t=10$, to emphasize color variations).

differences in categorical novelty, and not due to differences in image arousal.

The amygdala can habituate rapidly to repeated stimulus presentations (Breiter et al., 1996; Wright et al., 2001); therefore, we performed a post-hoc analysis to assess habituation of the novelty response in the amygdala and hippocampus (see Supplementary Materials). Both amygdala and hippocampal responses showed habituation across runs. However, the habituation effect was consistent across all stimulus types and the reported novelty effects were significant in each run. Thus, the present findings are not attributable to differential rates of habituation in the amygdala and hippocampus.

Whole-brain analysis

To provide a complete picture of the brain's response to novelty, we examined whole-brain responses to the two contrasts of interest (novel common>familiar, novel uncommon>novel common). Confirming the region of interest analyses, clusters in both the amygdala and hippocampus (anterior and posterior) both showed increased responses to novel common relative to familiar images. BOLD signal increased in a very large area encompassing both primary and secondary visual areas when viewing novel common compared to familiar images (Table 1). Other significant clusters included bilateral inferior frontal gyrus and cerebellar vermis.

For the comparison of novel uncommon relative to novel common images, there were significant bilateral amygdala clusters, but no activation in either hippocampus, again confirming the ROI analyses. As shown in Table 2, significant clusters were also found in the visual cortex, inferior and superior temporal gyrus, inferior frontal gyrus, inferior parietal lobe, cerebellum, and anterior cingulate.

We also examined response to novelty across the brain using the event-related analysis which controlled for image-specific differences in arousal. As with the supplemental region of interest analyses, the results from the whole-brain analyses controlling for arousal were very similar to the primary results presented in Table 2 (reported in Supplemental Tables 2 and 3).

Discussion

The present study illustrates the importance of distinguishing between different types of novelty. The amygdala and hippocampus demonstrated unique patterns of responses to two distinct types of novelty. Whereas the hippocampus showed a similar response to both contextual and categorical novelty, the amygdala was differentially sensitive to these two aspects of novelty. The results regarding the amygdala have two implications. First, the findings provide strong evidence that the amygdala responds to contextual novelty. Prior neuroimaging findings suggested that the amygdala responds to novel human faces (Schwartz et al., 2003; Wright et al., 2003), but the current results suggest that such responses are not specific to faces

Table 1
Significant whole-brain activations for novel common>familiar stimuli.

Cluster	Peak voxel					
Brain regions (hemisphere)	Cluster size	*p* value	*t* score	*x*	*y*	*z*
Lingual gyrus (R/L) Fusiform gyrus (R/L) Parahippocampal Gyrus gyrus (R/L)	5606	<.001	13.51	27	−45	−12
Inferior frontal gyrus (R)	28	<.001	3.53	39	6	30
Inferior frontal gyrus (L)	27	<.001	3.78	−42	3	30
Cerebellar vermis	21	<.001	3.91	0	−57	−36
Amygdala (L)	51	<.001	4.85	−21	−3	−15
Amygdala (R)	36	<.001	4.00	27	−3	−21
Hippocampus (L)	223	<.001	5.76	−18	−27	−9
Hippocampus (R)	173	<.001	6.03	24	−18	−12

Table 2
Significant whole-brain activations for novel uncommon>novel common stimuli.

Cluster	Peak voxel					
Brain regions (Hemisphere)	Cluster size	*p* value	*t* score	*x*	*y*	*z*
Lingual gyrus (R/L)	1207		7.81	12	−87	−9
Inferior temporal gyrus/BA37 (R) Fusiform Gyrus gyrus (R)	104	<.001	4.44	51	−42	−21
Inferior frontal gyrus (R)	85	<.001	3.93	51	36	0
Superior temporal gyrus (R)	57	<.001	3.74	42	−33	3
Inferior parietal lobule (R)	44	<.001	3.82	54	−30	27
Cerebellum anterior and posterior Lobes (R)	41	.001	3.18	15	−60	−30
Anterior cingulate/BA32 (R/L)	23	<.001	3.53	0	39	18
Amygdala (L)	7	.001	3.22	−27	0	−18
Amygdala (R)	4	.002	2.97	24	3	−21

and extend to other types of visual stimuli. Second, and most important, the amygdala appears especially sensitive to unusual stimuli, resulting in preferential processing of uncommon stimuli beyond the increased awareness afforded to contextually novel stimuli. The preferential processing interpretation is consistent with recent reports that the amygdala is engaged by unknown or ambiguous stimuli, such as uncertain outcomes (Hsu et al., 2005), and supports the view that the amygdala is involved in allocating resources to determine the attributes and potential impact of unknown stimuli (Whalen, 1998).

Unlike the amygdala, the hippocampus did not show an increased response to the novel uncommon stimuli, but showed a similar response to both contextual and categorical novelty. The hippocampal response to contextual novelty is consistent with prior studies demonstrating a critical role for the hippocampus in detecting novel events (Knight and Nakada, 1998) and in the contextual probability of an event occurring over time (Harrison et al., 2006; Strange et al., 2005). Our findings add to the literature by demonstrating that the hippocampal response to novel stimuli generalizes to unusual novel stimuli. However, unlike studies reporting a unique role for the anterior hippocampus in detecting contextually novel objects or events (Herry et al., 2007; Pihlajamaki et al., 2004; Strange et al., 1999), we found activation in both the anterior and posterior hippocampus.

In the whole-brain analyses, the strongest finding was the involvement of the primary and secondary visual areas in novelty detection for both common and unusual stimuli. This finding is not surprising given the amygdala's efferent connections to the visual system (Amaral et al., 2003). The enhanced activation of visual regions by novel stimuli parallels effects of emotional images (Lang et al., 1998). To the extent that these visual cortical responses are directed by the amygdala, the present results suggest that the amygdala's ability to direct attentional resources extends to novel images. However, we cannot rule out the possibility that these findings are driven by other regions or reflect a primary sensory process in visual cortex. Effective connectivity analysis (Friston, 1994) might further our understanding of the functional relationship between the amygdala and visual cortex.

We selected a block design for this initial study to provide increased detection power (Liu et al., 2001) using a paradigm previously used to demonstrate amygdala response to novel faces (Schwartz et al., 2003). An assumption of the block design is that all stimuli within a block are similar. However, stimuli can differ along multiple dimensions—such as novelty, valence, arousal, salience, and impact—which may each contribute to the brain's response to the stimuli. For example, in this study the novel uncommon images were rated as slightly more arousing than the novel common images. Several studies indicate that arousing stimuli induce amygdala activation (Kensinger and Schacter, 2006; Lewis et al., 2007), although the extent to which these activations relate to arousal versus valence, salience or impact, remains a matter of debate in the literature (Anders et al., 2008; Ewbank et al., 2009; Posner et al., 2009). An event-related design can control for these image-specific differences by including additional regressors in the model, although often at the cost of reduced detection power. This study used a block design to provide the initial evidence for the amygdala's response unique response to categorical novelty. Future studies could use an event-related design to further explore the effect of other stimulus features (e.g., salience, impact) on the amygdala's response to novelty.

The results from this study may have implications for research in temperament, personality, and psychiatric illness. Individual differences in response to novelty are a core part of temperament and personality, and extreme responses, such as neophobia and sensation-seeking, are characteristic of psychiatric illnesses including social anxiety, autism, schizophrenia, and substance abuse. Examination of individual differences in the brain's response to nonsocial novelty may provide new insights into both normal variation in personality and psychiatric illness.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.12.083.

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