It was not possible to parse out the effect of neutral valence in the context of high arousal, or the effects of negative or positive valence (vs. neutral) in the context of low arousal, because these combinations were not available within the standard IAPS stimulus set; nor does the IAPS stimulus set include high arousal neutral images. As a consequence, neutral valence and low arousal were necessarily confounded in this study. Twelve pictures were used for the familiar condition, and the remaining 120 pictures were used for the novel condition. Positive and negative pictures were equated for level of arousal [positive: $M = 5.50$ $SD = 0.74$; negative: $M = 5.69$, $SD = 0.79$; $t(86) = 1.18$, $p = .24$], as were the novel and familiar pictures [novel: $M = 5.04$, $SD = 1.15$; familiar: $M = 4.95$, $SD = 1.21$; $t(130) = .251, p = .80$].

Procedure

Prior to scanning, each participant completed a brief practice run outside the scanner to become familiar with the experimental task; practice images were not used in the experimental runs. The task was run using E-Prime experimental software (Psychology Software Tools, Pittsburgh, PA) on a PC, from which images were projected onto a screen in the magnet bore. Participants viewed images via a mirror mounted on the head coil.

The imaging paradigm consisted of five event-related fMRI runs. The first run was a familiarization run. Participants were familiarized to two images in each stimulus category (12 pictures total). The 12 IAPS images were each shown 10 times. Throughout four test runs, participants viewed each familiarized image a total of 10 times and each of the 120 novel images only once. During scanning, participants rated each image for how aroused it made them feel using a 3-point scale (1 = low, 2 = mid, 3 = high) and answered with a button response box. Each run was 340 sec in length and each image was presented for 3.5 sec, with a stimulus onset asynchrony that varied from 4 to 16 sec.

Image Acquisition

We used a Siemens Magnetom Trio Tim 3-T whole-body high-speed imaging device equipped for echo-planar imaging (EPI) (Siemens Medical Systems, Iselin NJ) with a 12-channel gradient head coil. Expandable foam cushions restricted head movement. After an automated scout image was acquired and shimming procedures were performed to optimize field homogeneity, high-resolution 3-D MP-RAGE sequences (TR/TE/flip angle = 2.53 sec/3.39 msec/7°) with an in-plane resolution of 1.0 × 1.0 mm, and 1.0 mm slice thickness were collected for spatial normalization and for positioning the slice prescription of the subsequent sequences. fMRI images with blood oxygenation level dependent (BOLD; Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, & Glynn, 1990) were acquired using a gradient-echo T2*-weighted sequence (TR/TE/flip angle = 2.0 sec/30 msec/90°). Prior to each scan, four scans were acquired and discarded to allow longitudinal magnetization to reach equilibrium. The gradient-echo functional images were collected in the same plane (33 coronal slices angled perpendicular to the AC/PC line) with the same slice thickness (5 mm; voxel size 3.12 × 3.12 × 5 mm), excitation order (interleaved), and phase encoding (foot-to-head). We used these parameters based on earlier work that suggested that the parameters helped minimize susceptibility in medial temporal lobe regions (Wright et al., 2001).

Magnitude of Amygdala Response: Anatomical ROI Analyses

Based on our a priori hypothesis that the amygdala plays a central role in the brain's affective workspace, we first conducted analyses focusing the magnitude of amygdala activation along the time course for each stimulus category. We used an anatomically based approach to conduct ROI analyses of functional data from the amygdala, using FSFAST (http://surfer.nmr.mgh.harvard.edu). We applied automated subcortical segmentation methods to the native 3-D MP-RAGE structural images for each subject to create anatomically defined amygdala ROIs (Fischl et al., 2002), and individual amygdala volumes were also calculated. We manually verified these amygdala ROIs according to our previously published protocols (Wright, Dickerson, Feczko, Negeira, & Williams, 2007; Wedig et al., 2005). The anatomically defined amygdala ROIs were registered to fMRI data, and BOLD signal was extracted for each participant. To explore the details of the time course at the amygdala in both groups, functional data for each condition were modeled using a finite impulse response (FIR) model beginning at 4 sec before stimulus onset, and utilizing 2-sec bins. We estimated the duration of the hemodynamic response to be 16 sec. Percent signal change for combinations of valence, arousal, and novelty versus baseline (fixation) was calculated. Because individuals of the older group have smaller amygdala volumes [right: young, $M = 1798.1$ (mm^3), $SD = 197.1$; older, $M = 1568.2$, $SD = 282.4$; $t = 2.98$, $p = .005$; left: young, $M = 1670.6$, $SD = 282.4$; older, $M = 1406$, $SD = 244.4$; $t = 3.69, p = .001$], and this directly influences amygdala signal, we adjusted the functional data using individual amygdala volume as a covariate in all analyses.

To examine age-related differences in the magnitude of the BOLD response within the amygdala at different points along the time course, we analyzed our repeated measures design using a multivariate analysis of variance (MANOVA) with multivariate effect estimation (Wilk's, Pillai's, etc.). We chose this multivariate approach (where responses were modeled as individual dependent measures) because the sphericity varied enough in at least three time points within the amygdala time course that the statistical assumption of sphericity was violated (making a standard repeated measures ANOVA not advisable; Misangyi, LePine, Algina, & Goeddeke, 2006; Tabachnick & Fidell, 2006, for examples of using this method, see Nitschke

et al., 2006; Tilman, Hill, & Lehman, 2006; Tilman, Reich, & Knops, 2006; Koekkoek et al., 2003). We conducted four different repeated measures MANOVAs each for the left and right amygdala to investigate all important effects of interest given that we could not fully cross (balance) valence and arousal due to stimulus limitations.

Curve Fitting Analysis

We conducted additional curve fitting analyses on the amygdala time course data to determine group differences in time course shape. This curve fitting analysis provided additional information about "how" the hemodynamic curve differed for younger and older participants by estimating and comparing parameters obtained by fitting a hemodynamic function to actual time course data. The time course data were fitted with the simplified gamma probability density function that is commonly used as canonical hemodynamic function in neuroimaging studies, given by

$$y = c \times \text{gampdf}((x-d),a,b) = \left(cx^{a-1}e^{x/b}\right)/[b^a\Gamma(a)]$$

where Γ is the gamma function, c is the magnitude parameter (i.e., equivalent to beta coefficient in GLM analysis), d is delay from the onset of the event, a is the "shape" parameter (similar to kurtosis; the larger the a is the broader distribution the function has), b is another scale parameter that affects the magnitude. In our analyses, b was fixed at 1.25 (the value used in FSFAST as a default setting), and a best-fit gamma probability density function was fit to the actual FIR time course data. Parameters a, c, and d were estimated with 95% confidence intervals. In this analysis, we used Curve Fitting Toolbox in Matlab (MathWorks, Natick, MA).

Functional Connectivity Analyses

We conducted functional connectivity analyses to explore how the group difference of time course activation in the amygdala was correlated with activation in other brain areas that belong to the neural reference space for affect [e.g., both sides of the amygdala (AMG), anterior insula (AI), medial posterior OFC at Brodmann's area 11 to 13 (OFC), thalamus (Thal), hippocampus (Hc), fusiform gyrus (FG), inferior frontal gyri; Brodmann's area 45 to pars triangularis (IFGtri), and Brodmann's area 47 to pars orbitalis (IFGorb), ventromedial prefrontal cortex (vmPFC), and ventral ACC (vACC) (Kober et al., 2008; Barrett, Mesquita, Ochsner, & Gross, 2007)]. First, for the purpose of merely extracting the affect-related ROIs, all events versus fixation contrast were estimated by GLM with a canonical hemodynamic response using SPM5, in each group, independently across whole brain (available from the first author on request). Then, using a conjunction analysis, we localized commonly activated areas of two event-related activation maps (all vs. fixation, $p < .05$ with correction of false discovery rate) of both young and older groups. These common activation areas were further restricted by the structure data of the amygdala and other emotion-related regions adopted from the Automated Anatomical Labeling (AAL) dataset (Tzourio-Mazoyer et al., 2002) using PickAtlas software (Maldjian, Laurienti, Kraft, & Burdette, 2003). The regional mean % signal changes across all voxels in an ROI were calculated. Using FIR estimation, all the time course data in each ROI were extracted for each stimulus type separately. Correlation analyses of stimulus-specific time course data were conducted between the right or left amygdala and other ipsilateral ROIs if there was activation or deactivation in these areas, and correlation coefficients were compared between two groups. Using this method, correlation coefficients reflect the similarity of both the magnitude of the peak response as well as the overall pattern of event-related hemodynamic response in two regions.

RESULTS

Behavioral Measures

Memory and Personality Data

Older individuals had decreased CVLT scores compared to younger participants, indicating decreased memory function (see Table 1). The scores in older participants were very close to those in other normative aged samples, however, indicating that they were experiencing normal decrements in memory with age (e.g., Delis et al., 2000; Hu et al., 1999). Young and elderly participants did not differ on the affectively relevant personality dimensions of emotional stability (neuroticism) and extraversion, although younger individuals scored significantly higher on intellect/imagination (openness to experience).

Arousal Ratings of IAPS Pictures

We conducted Novelty (novel, familiar) × Valence (negative, positive, neutral) × Age (young, older) repeated measures ANOVA on subjective arousal rating of IAPS pictures. All participants rated negative pictures as significantly more arousing than positive images, which in turn were more arousing than neutral images (see Figure 1) [$F(1.71, 68.28) = 124.77, p < .0001$, Greenhouse–Geisser correction]. Older individuals found negative pictures significantly less arousing than did young individuals (see Figure 1) [repeated ANOVA, Valence × Age, $F(2, 80) = 3.18, p = .047$].

Despite being equated for arousal at the outset, all participants rated novel pictures as more arousing than familiar [novelty effect: $F(1, 40) = 31.27, p < .0001$]. Older individuals found novel pictures significantly less arousing than did young individuals, however (see Figure 1) [Novelty × Age: $F(1, 40) = 5.99, p = .019$]. This was particularly true for valenced images as old and young participants found novel, neutral pictures equally arousing [$F(1, 40) = 2.133, p = .152$].

Table 1. Comparison of Prescanning Tests between the Young and the Older Group

	YNG		*OLD*			
	Mean	*SD*	*Mean*	*SD*	*t*	*Significance (two-tailed)*
California Verbal Learning Test						
List A Total Recall	62.8	11.5	49.6	10.1	3.67	.001*
List A Total Recall Intrusion	0.3	0.6	0.7	1.3	−1.32	.196
List B Total Recall	8.8	2.7	5.8	1.9	4.03	<.001*
List B Recall Intrusion	0.1	0.3	0.3	0.6	−1.26	.216
Short Delay Free Recall	13.9	2.8	9.8	3.9	3.54	.001*
Short Delay Free Recall intrusion	0.0	0.0	0.3	0.4	−2.24	.031*
Short Delay Cued Recall	14.0	2.4	10.7	3.3	3.37	.002*
Short Delay Cued Recall intrusion	0.3	0.5	0.9	1.1	−1.83	.076
Long Delay Free Recall	13.9	2.4	9.6	3.7	3.91	<.001*
Long Delay Free Recall intrusion	0.0	0.0	0.6	0.8	−2.82	.008*
Long Delay Cued Recall	13.9	2.6	10.2	3.4	3.55	.001*
Long Delay Cued Recall intrusion	0.1	0.4	1.0	1.2	−2.67	.012*
Recognition Performance	22.7	12.6	31.4	14.9	−1.83	.077
International Personality Item Pool						
Surgency or Extraversion	63.4	3.9	61.8	5.5	1.04	.304
Agreeableness	67.3	8.6	61.4	13.4	1.67	.103
Conscientiousness	60.3	4.5	59.9	6.8	0.24	.814
Emotional Stability	49.8	7.1	50.6	6.4	−0.37	.712
Intellect or Imagination	64.2	5.2	60.6	6.1	2.07	.044*

YNG = younger group; OLD = older group.

Subjective arousal ratings also showed a significant three-way Novelty (novel, familiar) × Valence (negative, positive, neutral) × Age (young, older) interaction [$F(2, 40) = 5.71, p = .005$]. To clarify the three-way interaction, we used a Novelty × Age stratified ANOVA for positive, negative, and neutral pictures separately. We found that there was a significant Novelty × Age interaction for positive picture condition [$F = 17.73, p < .001$], but this effect did not hold for negative and neutral picture conditions [$F = .507, p = .481$ for negative, $F = 2.133, p = .152$ for neutral]. The analyses suggested that, taken together with Figure 1, younger individuals found novel images more arousing than did older individuals, and older individuals found positive familiar images more arousing than did young individuals.

To confirm the effect of stimulus arousal level on subjective arousal ratings, we performed Age × Arousal ANOVA for subjective arousal ratings. There was a main effect of image arousal on subjective arousal ratings, such that all participants experienced high arousal pictures as significantly more arousing than mid, which were more arousing than low [$F(1, 40) = 86.65, p < 001$ for valenced images; $F(1, 40) = 69.20, p < 001$ for neutral images]. There were marginally significant age-related difference in the stimulus arousal effects for valenced images (Table 2) [Age × Arousal interaction: $F(1, 40) = 3.51, p = .068$], suggesting that older individuals found high arousal valenced images less arousing than did young individuals. There was no significant age-related difference of stimulus arousal effect for neutral images, however [$F(1, 40) = 0.459, p = .502$].

Magnitude of Amygdala Response

Because of stimulus constraints (it was not possible to fully cross-valence and arousal), two different repeated measures MANOVAs were necessary to examine age-related differences in amygdala's response to novelty and valence. First, we conducted Novelty (novel, familiar) × Valence (positive, negative, neutral) × Time point (1–8) × Age (young, older) repeated measures MANOVA to examine age-related novelty and valence effects on the amygdala activation. A second analysis was Novelty (familiar, novel) × Time point (1–8) × Age (young, elderly) repeated measures MANOVA for neutral pictures to clarify age-related differences in

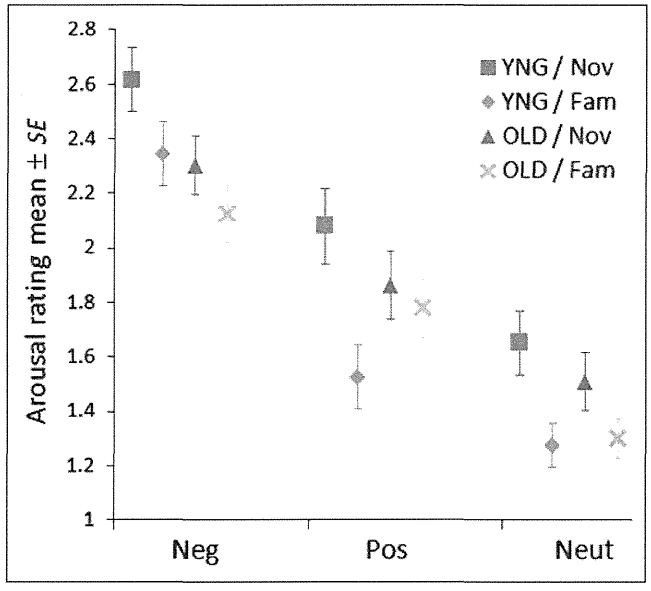

Figure 1. Rating of arousal level of each valence of IAPS pictures. Mean ± *SE* of arousal ratings of IAPS pictures during scanning are plotted in each valence of the stimuli (Neg = negative; Pos = positive; Neut = neutral). YNG = younger group; OLD = older group; Nov = novel condition; Fam = familiar condition.

amygdala responses to novel versus familiar images that were neutral in hedonic valence. To examine age-related differences in amygdala response to novelty and picture arousal level, we conducted Novelty (novel, familiar) × Arousal (high, mid) × Time point (1–8) × Age (young, older) repeated measures MANOVA for amygdala response to valenced images, and Novelty (novel, familiar) × Arousal (mid, low) × Time point (1–8) × Age (young, older) repeated measures MANOVA for amygdala response to neutral images.

FIR Analyses of Age-related Novelty and Valence Effects on the Amygdala Activation

When examining the overall amygdala response, there were no age-related differences in amygdala responses to novelty or valence; there was no Novelty × Age interaction for right amygdala responses [$F(1, 38) = 1.06$, $p = .311$], nor for left amygdala responses [$F(1, 38) = 1.39$, $p = .245$]. There was no Valence × Age interaction for right amygdala responses [$F(2, 37) = 1.79, p = .182$], nor for left amygdala responses [$F(2, 37) = 0.86, p = .430$]. For all participants, both valence [$F(2, 37) = 8.32, p = .001$] and novelty [$F(1, 38) = 5.46$, $p = .025$] significantly engaged the right amygdala. In addition, both valence [$F(2, 37) = 4.12$, $p = .024$] and novelty [$F(1, 38) = 13.97$, $p = .0006$] engaged the left amygdala.[1]

To examine age-related differences in the magnitude of the amygdala along its time course, we conducted a Novelty (familiar, novel) × Valence (positive, negative, neutral) × Time point (1–8) × Age (young, elderly) repeated measures MANOVA on the BOLD response within the right and left amygdala ROIs. Time courses are illustrated in Figure 2. The time course patterns in both left and right amygdala were similar; only the data in the left amygdala are shown. There was an age-related difference in the right and left amygdala time course for novelty [Novelty × Time point × Age: right, $F(7.32) = 4.01$, $p = .003$; left, $F(7, 32) = 2.46, p = .039$], such that younger and older individuals showed a different amygdala time course when viewing novel images. In particular, older (vs. younger) individuals have weaker amygdala responses before and after the peak, leading to a narrower and sharper time course (also see Curve Fit Analysis). The overall Valence × Time point × Age interaction was not significant in the right amygdala, $F(14, 25) = 1.65, p = .133$, nor in the left amygdala, $F(14, 25) = 1.45, p = .200$, such that there was no age-related significant difference in the amygdala time course when viewing positive or negative images, although older individuals did appear to show a similar "peakier" response in their amygdala response to negative and positive images when compared to younger individuals.

The four way Novelty × Valence × Time point × Age interaction was not statistically significant in the right amygdala [$F(14, 25) = 0.70, p = .75, \eta_p^2 = .282$], but was marginally significant in the left amygdala [$F(14, 25) = 2.02, p = .061$, $\eta_p^2 = .531$]. From Figure 2, this interaction in the left amygdala appeared to be driven by "peakier" amygdala response in the older group than in the young group, particularly in response to novel positive and neutral images rather than to novel negative images. To check this finding, we added a Valence × Time point × Age stratified repeated MANOVA for left amygdala BOLD response only for the novel pictures; we confirmed this marginally significant three-way interaction [$F(14, 25) = 2.04, p = .058$, $\eta_p^2 = .533$], suggesting that the hemodynamic curves were different for young and older participants, particularly in response to novel positive and neutral images.

Further, we did stratified ANOVAs Novelty (novel, familiar) × Age (young, older) in each time point separately, and found significant Novelty × Age interactions at the time points of 2–4 sec [$F(1, 38) = 5.97, p = .02, \eta_p^2 = .14$],

Table 2. Mean (*SE*) of the Subjective Arousal Ratings of Different Arousal Levels of IAPS Images in Each Age Group

	Age Group	
Images	*YNG*	*OLD*
Valenced		
High arousal	2.31 (0.11)	2.13 (0.10)
Mid arousal	1.98 (0.10)	1.91 (0.09)
Neutral		
Mid arousal	1.64 (0.11)	1.61 (0.10)
Low arousal	1.29 (0.09)	1.20 (0.08)

YNG = young group; OLD = older group.

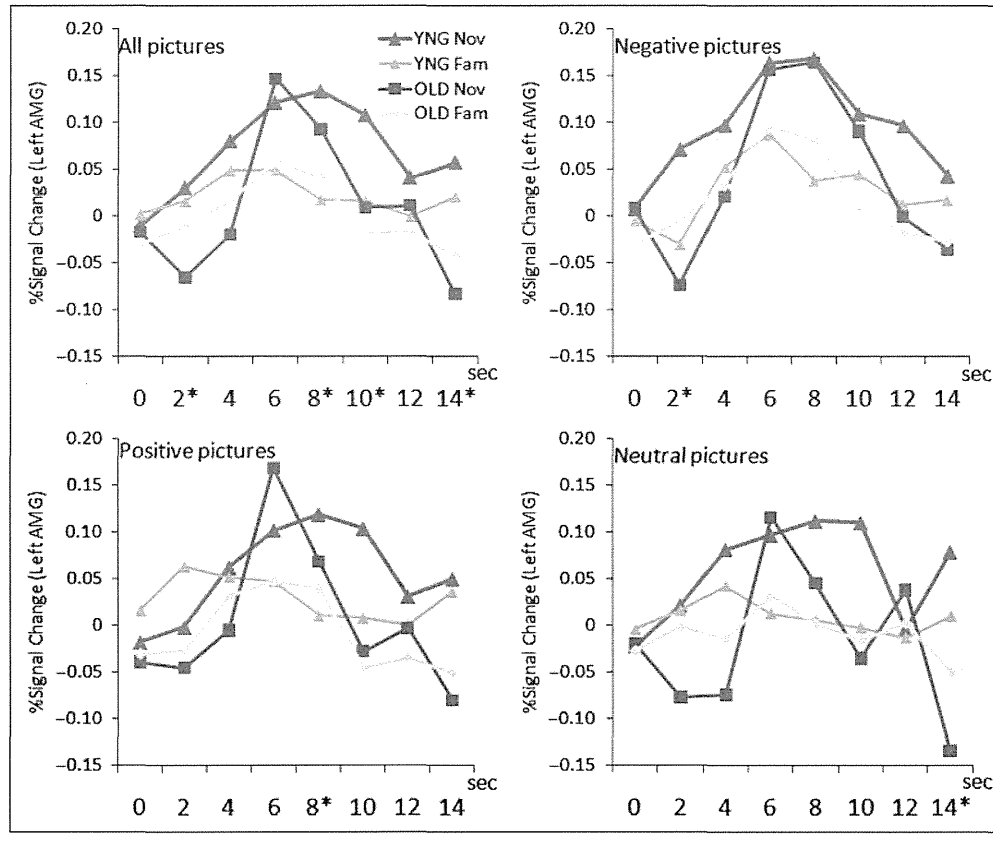

Figure 2. Age-related difference of hemodynamic time course in FIR analysis in the left amygdala. Event-related time course of BOLD response (% signal change) in each condition (Valence × Novelty) in two age groups. The right amygdala also showed a similar pattern so only the time course in the left amygdala was illustrated. Red = young group (YNG); green = older group (OLD). The four lines colored in red and green show response to novel (Nov) and familiar (Fam) images in the young and the older groups (Nov/YNG, Nov/OLD, Fam/YNG, Fam/OLD), which are displayed on each all, negative, positive, and neutral picture condition panels. Asterisk (*) shows significant Novelty × Age interaction ($p < .05$) in each time bin (TR = 2 sec).

8–10 sec [$F(1, 38) = 4.41, p = .04, \eta_p^2 = .10$], 10–12 sec [$F(1, 38) = 3.88, p = .06, \eta_p^2 = .09$], and 14–16 sec [$F(1, 38) = 4.67, p = .04, \eta_p^2 = .11$] in response to all three-valence images in the left amygdala; 2–4 sec in response to negative images in the right amygdala [$F(1, 38) = 5.16, p = .029, \eta_p^2 = .12$]; 2–4 sec in response to negative images in the left amygdala [$F(1, 38) = 10.1, p = .003, \eta_p^2 = .21$]; 8–10 sec to positive images in the left amygdala [$F(1, 38) = 4.27, p = .046, \eta_p^2 = .10$]; and 14–16 sec to neutral images in the left amygdala [$F(1, 38) = 6.72, p = .013, \eta_p^2 = .15$]. Taken together with Figure 2, the analyses appeared to show that the group differences of response to novel pictures occurred in early and late phases in the time course.

Age-related Differences in Amygdala Response to Novel vs. Familiar Neutral Images

To further investigate age-related differences within the amygdala time course in response to novelty, we conducted a Novelty (familiar, novel) × Time point (1–8) × Age (young, elderly) repeated measures MANOVA on the BOLD response to the neutral images, within the right and left amygdala ROIs. There was an age-related difference in the left amygdala time course for novelty [Novelty × Time point × Age: $F(7.32) = 2.65, p = .028$]. This indicates that, even upon observing only neutral images, older individuals had a narrow and sharper amygdala time course to novelty when compared to younger individuals. In the right amygdala, there was no Novelty × Time point × Age interaction [$F(7.32) = 1.23, p = .32$].

FIR Analyses of Age-related Novelty and Picture Arousal Effects on the Amygdala Activation

To address the question of whether novelty and picture arousal level interact to produce the neural response in the amygdala, we conducted Novelty (novel, familiar) × Arousal (high, mid) × Time point (1–8) × Age (young, older) repeated measures MANOVA for the right and the left amygdala response to valenced images, and Novelty (novel, familiar) × Arousal (mid, low) × Time point (1–8) × Age (young, older) repeated measures MANOVA for the right and the left amygdala response to neutral images. We found significant Novelty × Arousal × Time point × Age interactions for the left amygdala response to valenced images [$F(7, 32) = 2.43, p = .041, \eta_p^2 = .35$], and to neutral images [$F(7, 32) = 2.82, p = .021, \eta_p^2 = .38$], but not for the right amygdala response to valenced images [$F(7, 32) = 1.73, p = .13, \eta_p^2 = .28$], nor to neutral images [$F(7, 32) = 0.42, p = .88, \eta_p^2 = .09$]. Overall, the results were the same as the analyses with novelty and valence; older individuals showed a peakier amygdala response to novel pictures of higher levels of arousal when compared to younger individuals who showed a more sustained response across ~10 sec. The figures are not shown here, and the details of the findings and figures are available from the first author by request.

Curve Fit Analysis

On inspecting the hemodynamic curves from the FIR analysis, older individuals appeared to have a "peakier" amygdala time course when compared to younger individuals, particularly in response to novel stimuli. This was confirmed by an additional curve fitting analysis, showing that older individuals showed a different amygdala time course in response to novel pictures when compared to young individuals (Figures 3 and 4).

The simplified gamma probability density function hypothesized in the Methods section fits the observed FIR time course data quite well; all adjusted $R^2 > .9$ and all root-mean-squared-error (RMSE) < .05 (suggested by

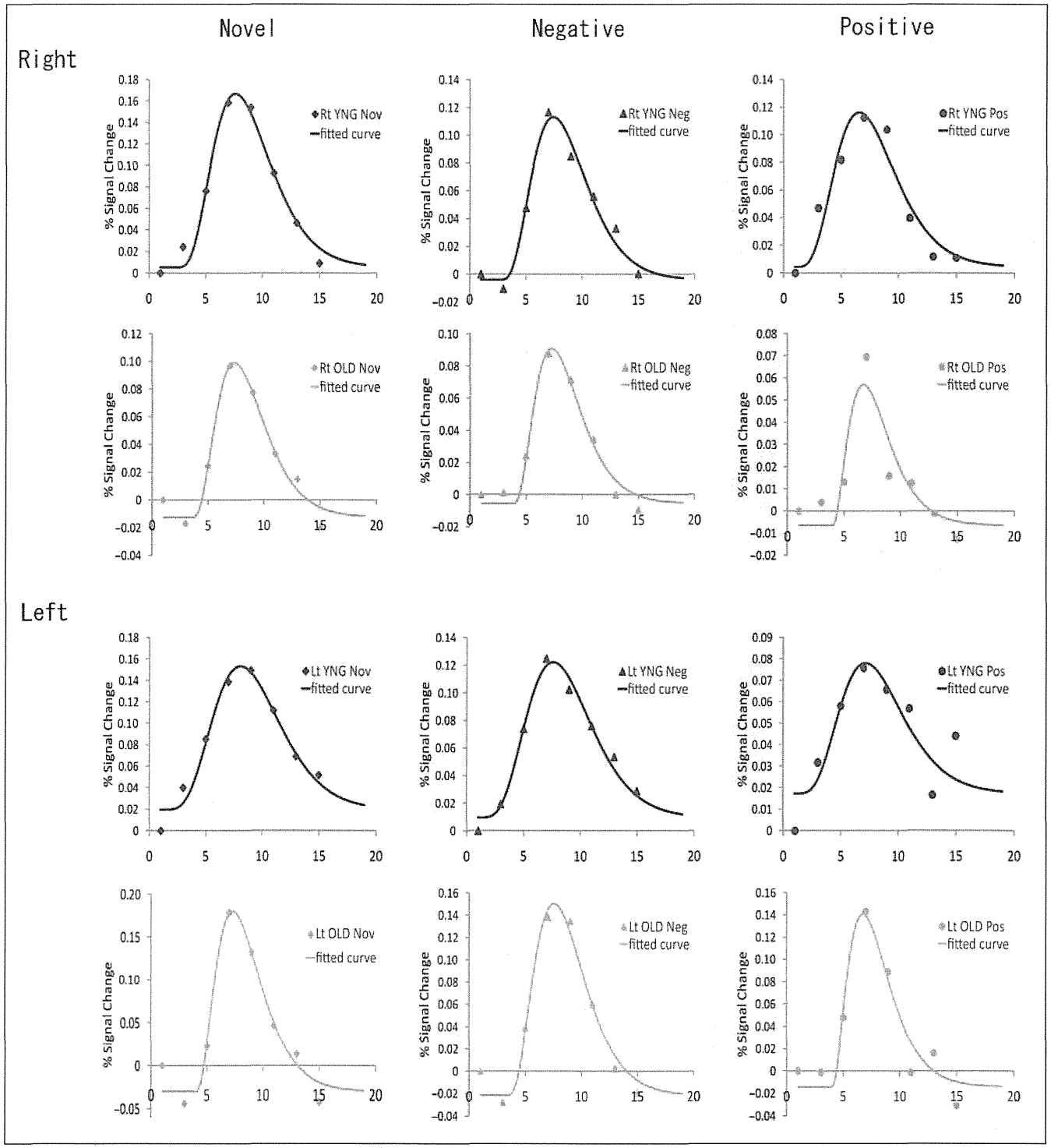

Figure 3. The time course of BOLD response to novel, negative, and positive pictures and fitted curves in curve fitting analyses. Rt = right; Lt = left; red dots and curve = young group; blue dots and curve = older group. The left column = novel condition; middle column = negative condition; right column = positive condition.

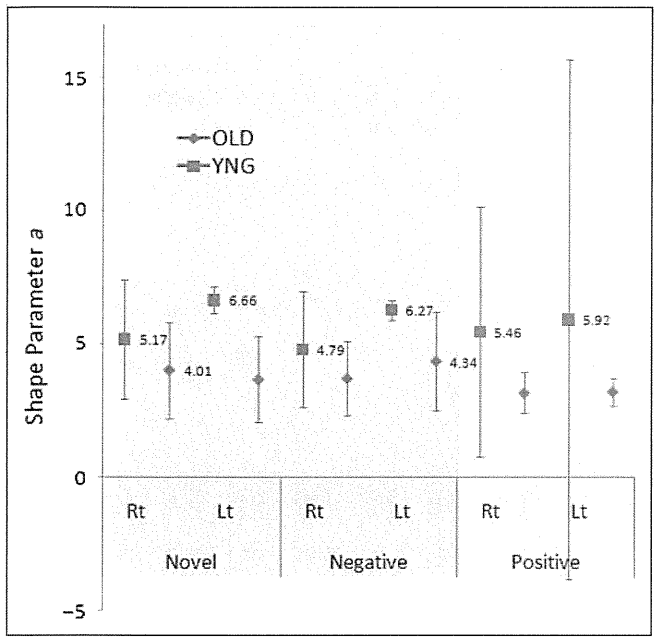

Figure 4. Shape parameter *a* in the curve fitting analyses in the novel, negative, and positive condition in the right/left amygdala. BOLD responses produced by FIR analyses in the right and left amygdala were fitted by gamma probability density function with three variable parameters of delay from time 0, height, and shape (broadness). The graph shows shape parameter *a* in each younger (YNG) and older (OLD) group in novel, negative, and positive condition. Upper = FIR data and fitting line; Lower = estimated value and 95% confidence interval (95% CI) of shape parameter *a* in both groups.

Browne & Cudeck, 1992). Table 3 shows the mean and 95% confidential interval of estimated shape parameter *a* for the BOLD time course in novel, negative, and positive conditions in the right and left amygdala. In these analyses, we found that older individuals had lower estimated *a* than that of the younger group, indicating that the older group had a peakier hemodynamic response to novel and negative pictures in the left amygdala. There was no group difference of parameter *a* in response to positive images in the left amygdala, or to any images in the right amygdala. Also, we did not observe any statistical age-related difference of delay (*d*) and height parameter (*c*).

Additionally, to check if this age-related difference of shape of hemodynamic time course was specific for the amygdala, we compared the hemodynamic time courses for the younger and older groups in other brain areas such as left medial posterior OFC, thalamus, hippocampus, fusiform gyrus, inferior frontal gyri pars triangularis, and inferior frontal gyri pars orbitalis. We also did curve fitting analyses in each ROI on BOLD response to novel stimuli. We did not find any age-related differences of parameter *a* similar to what were observed in the amygdala (Table 4). This suggests that not all hemodynamic responses across whole-brain areas show an age-related difference in time course shape difference, indicating that hemodynamic time course difference in the amygdala was not due to a general change in vasculature with aging.

Table 3. Estimated Mean and Upper/Lower Bound of 95% Confidence Interval of Shape Parameter *a* in Curve Fitting Analysis

	YNG			*OLD*		
	Mean	*$LoCI_{95}$*	*$UpCI_{95}$*	*Mean*	*$LoCI_{95}$*	*$UpCI_{95}$*
Right AMG						
Nov	5.17	2.94	7.41	4.01	2.21	5.81
Neg	4.79	2.62	6.96	3.70	2.30	5.11
Pos	5.46	0.76	10.17	3.17	2.39	3.95
Left AMG						
Nov	**6.66**	**6.17**	7.14	**3.66**	2.04	**5.27**
Neg	**6.27**	**5.90**	6.63	**4.34**	2.49	**6.19**
Pos	5.92	−3.85	15.70	3.20	2.67	3.73

YNG = younger group; OLD = older group; AMG = amygdala; Nov = novel condition; Neg = negative condition; Pos = positive condition; $LoCI_{95}$ = lower bound of 95% confidence interval; $UpCI_{95}$ = upper bound of 95% confidence interval.

Bold type: YNG mean > OLD $UpCI_{95}$ and OLD mean < YNG $LoCI_{95}$.

For novel conditions, mean *a* = 3.66 in older < $LoCI_{95}$ = 6.17 in younger, mean *a* = 6.66 in younger > $UpCI_{95}$ = 5.27 in older; for negative conditions, mean *a* = 4.34 in older < $LoCI_{95}$ = 5.90 in younger, mean *a* = 6.27 in younger > $UpCI_{95}$ = 6.19 in older.

Functional Connectivity Analysis

Functional connectivity analyses indicated that the amygdala of older individuals had a somewhat different pattern of correlated activity than the amygdala of younger individuals when responding to novelty. Correlation coefficients in novel versus familiar picture conditions were compared between the two groups (Figure 5), and those reported

Table 4. Mean and Upper/Lower Bound of Confidential Interval of Shape Parameter *a* in Curve Fitting Analysis in Affect-related ROIs in the Left Hemisphere

	YNG			*OLD*		
	Mean	*$LoCI_{95}$*	*$UpCI_{95}$*	*Mean*	*$LoCI_{95}$*	*$UpCI_{95}$*
OFC	5.26	3.02	7.51	4.60	1.89	7.31
Thal	5.16	3.43	6.90	4.51	3.15	5.86
Hc	4.17	2.55	5.80	2.97	1.57	4.37
FG	2.73	2.43	3.03	4.12	2.89	5.36
IFG tri	4.67	3.00	6.34	5.18	3.38	6.98
IFG orb	4.90	3.21	6.59	3.36	1.57	5.15

OFC = posterior orbito-frontal cortex at Brodmann's area 11 to 13; Thal = thalamus; Hc = hippocampus; FG = fusiform gyrus; IFGtri = inferior frontal gyrus (Brodmann's area 45 to pars triangularis); IFGorb = inferior frontal gyrus (Brodmann's area 47 to pars orbitalis); $LoCI_{95}$ = lower bound of 95% confidence interval; $UpCI_{95}$ = upper bound of 95% confidence interval.

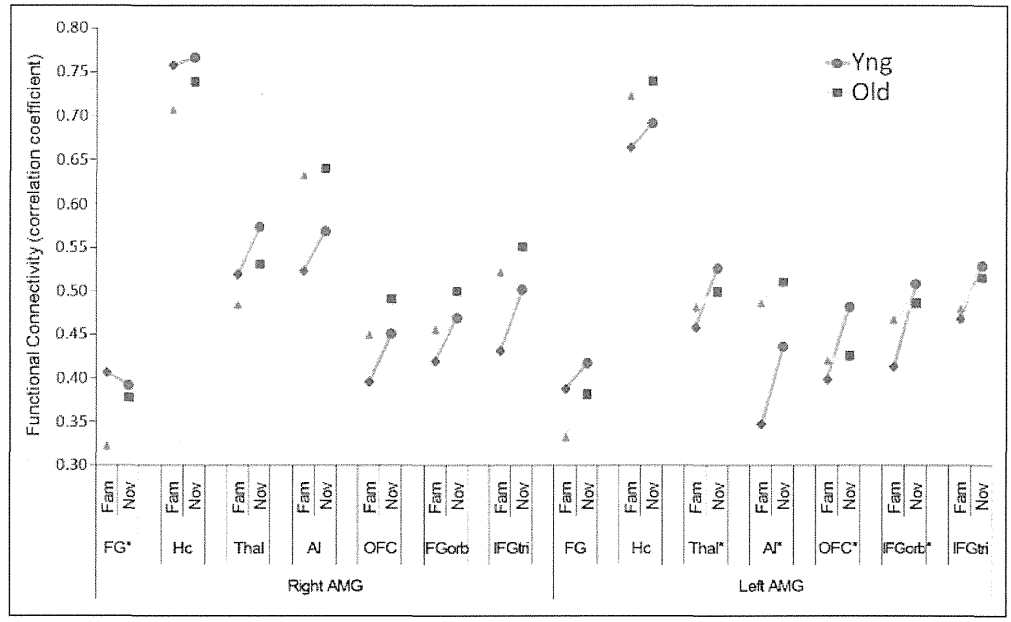

Figure 5. Functional connectivity between amygdala and other ROI. Correlation coefficients of event-related BOLD response between the amygdala and other emotion-related ipsilateral ROIs in novel (Nov) and familiar (Fam) conditions. Contralateral connectivity showed similar pattern so only ipsilateral connectivity was shown. FG = fusiform gyrus; Hc = hippocampus; Thal = thalamus; AI = anterior insula; OFC = orbito-frontal cortex; IFGorb = inferior frontal gyrus (pars orbitalis); IFGtri = inferior frontal gyrus (pars triangularis); AMG = amygdala. Red circle/diamond and line = young group (YNG); green triangle/square and line = older group (OLD). The flesh-colored ROI and asterisk (*) show a connectivity with significant Novelty × Age interaction ($p < .05$).

were significant according to a Novelty (novel, familiar) × Age (young, older) interaction at $p < .05$. Only ipsilateral connections (i.e., right amygdala–right ROIs, and left amygdala–left ROIs) are presented because the patterns of contralateral connections were similar.

To test the interactive effect of valence and age on the functional connectivity in response to novel (vs. familiar) pictures, estimates of functional connectivity in response to novel/negative, novel/positive, novel/neutral, familiar/negative, familiar/positive, and familiar/neutral images were first calculated. Next, these estimates of connectivity (correlation coefficients) were entered into Novelty (novel, familiar) × Valence (negative, positive, neutral) × Age (young, older) repeated ANOVA. The results are presented in the Figure 5. Novelty increased the functional connectivity between the amygdala and almost every ipsilateral ROI; for novel pictures, the right amygdala showed greater functional connectivity with the right hippocampus [$F(1, 39) = 5.56, p = .024$], the right thalamus [$F(1, 39) = 10.95, p = .002$], the right anterior insula [$F(1, 39) = 4.54, p = .039$], right medial/posterior OFC [$F(1, 39) = 8.68, p = .005$], the right inferior frontal gyrus (pars orbitalis) [$F(1, 39) = 8.95, p = .005$], and the right inferior frontal gyrus (pars triangularis) [$F(1, 39) = 15.42$, $p < .001$]. Similarly, the left amygdala showed greater functional connectivity with the left fusiform gyrus [$F(1, 39) = 4.86, p = .033$], the left hippocampus [$F(1, 39) = 8.59, p = .006$], the left thalamus [$F(1, 39) = 12.76, p = .001$], the left anterior insula [$F(1, 39) = 12.24, p = .001$], left medial/posterior OFC [$F(1, 39) = 7.09, p = .011$], the left inferior frontal gyrus (pars orbitalis) [$F(1, 39) = 11.12$, $p = .002$], and the left inferior frontal gyrus (pars triangularis) [$F(1, 39) = 10.84, p = .002$]. Functional connectivity did not vary by the valence of the pictures, and the Novelty × Valence interaction did not reach statistical significance.

Furthermore, we found a significant Novelty × Age interaction for the connectivity between the left amygdala and the left thalamus [$F(1, 39) = 4.31, p = .045, \eta_p^2 = .10$], the left anterior insula [$F(1, 39) = 4.20, p = .047, \eta_p^2 = .10$], left medial/posterior OFC [$F(1, 39) = 5.63, p = .023, \eta_p^2 = .13$], and the left inferior frontal gyrus (pars orbitalis) [$F(1, 39) = 5.04, p = .031, \eta_p^2 = .11$]. In response to novel (vs. familiar) pictures, younger individuals showed greater functional connectivity than did older individuals between the left amygdala and the left thalamus, anterior insula, medial/posterior OFC, and inferior frontal gyrus (pars orbitalis). In contrast, older individuals showed enhanced connectivity between the right amygdala and the right fusiform gyrus; a significant Novelty × Age interaction [$F(1, 39) = 4.91, p = .033, \eta_p^2 = .11$]. This pattern of functional connectivity suggests that the frontal/orbital areas might be involved in sustaining amygdala response in younger individuals.

Both ventromedial prefrontal cortex and ventral anterior cingulate cortex (bilaterally) showed a decrease in activation from fixation baseline in response to positive images (replicating Leclerc & Kensinger, 2008), but we also observed deactivations in response to negative and novel images. Furthermore, the hemodynamic time courses in these two regions were weakly correlated with the amygdala time course ($r = 0.0–0.2$; data not shown). In functional connectivity analysis, correlations between activation and deactivation hemodynamics are difficult to meaningfully interpret from a methodological standpoint,

and so the results of this functional connectivity analysis are not shown here but are available upon request.

DISCUSSION

Our findings clearly indicate that novel stimuli are affectively significant and engage the amygdala in a robust way. This novelty effect was not accounted for by the arousing or valenced nature of the stimuli, as was exhibited even with neutral images. The idea of novelty as a stimulus property with affective salience is consistent with studies in which the amygdala habituates even to very evocative stimuli (e.g., Wright et al., 2001; Fischer, Furmark, Wik, & Fredrikson, 2000), and by animal studies showing that amygdala lesions disrupt normal responses to novelty in primates (e.g., Mason, Capitanio, Machado, Mendoza, & Amaral, 2006; Prather et al., 2001; Burns, Annett, Kelley, Everitt, & Robbins, 1996; for reviews, see Petrides, 2007; Knight & Grabowecky, 1999). Together, these findings shape an emerging view that the amygdala's function is not to represent negativity or valence per se, but rather to mark the salience of a stimulus and modulate other brain areas to increase the processing of that stimulus to gain information for future use (e.g., Ewbank, Barnard, Croucher, Ramponi, & Calder, 2009; Wedig et al., 2005; Anderson & Phelps, 2001; for a discussion, see Barrett & Bliss-Moreau, 2009; Duncan & Barrett, 2007a, 2007b). This view is also consistent with the view that the amygdala is a key brain structure that is involved in evaluating an object for its goal relevance (Sander, Grafman, & Zalla, 2003).

We did not find age differences of the peak magnitude of the hemodynamic response in amygdala to any evocative images, indicating that, at least in one sense, affective processing within the amygdala, including responsiveness to novelty, is preserved in older people. These results are consistent with prior research showing no age-related changes in novelty processing (Wright et al., 2006, 2008), suggesting that salience (Carstensen & Turk-Charles, 1994) or vigilance (Whalen, 2007) is maintained across the lifespan. These findings are in line with the observation that the amygdala is one of the regions which is relatively structurally preserved with aging when compared to many other brain regions (e.g., West, 1996; Moscovitch & Winocur, 1995; Daigneault & Braun, 1993). Our findings differ from those previously published studies that reported reduced amygdala activation to negative images in older individuals, however, for a number of reasons. One of the possible reasons is that we used FIR analyses to examine our event-related BOLD data, whereas prior studies have used an SPM canonical hemodynamic function (e.g., Mather et al., 2004). The remarkable difference of the shape of the hemodynamic time course in older (vs. younger) individuals that we discovered suggests that a canonical hemodynamic function might provide a worse fit to the actual hemodynamic pattern in older individuals, resulting in a lower estimate of activation (i.e., a lower correlation between actual amygdala response and hypothetical gamma curve). This valence effect in aging remains to be tested with future studies.

Importantly, our results demonstrated age-related difference in the shape of the hemodynamic time course of the amygdala, particularly in response to the novel stimuli that have not previously been reported; older people showed "peakier" hemodynamic response when compared to younger individuals. In previous methodological papers, age-related changes of hemodynamic response were inconclusive (e.g., the rise time of the fMRI signal in motor cortex increased with age during a 10-sec hand-squeezing task, Taoka et al., 1998; spatial extent of activation in older people did not differ from that of young people for a photic stimulation task, Ross et al., 1997; no highly consistent age difference exists in the shape of hemodynamic responses in primary sensorimotor cortex, D'Esposito et al., 1999; and sustained event-related BOLD effect even after the peak in the older group, Aizenstein et al., 2004). These methodological studies indicate the age-related time course difference of fMRI hemodynamic responses may depend on the situations and experimental paradigms, is probably brain region specific, and might not be a general property of the aging brain.

There are three possible ways to explain the origins of age-related amygdala time course differences found in the present study. The first is vascular effects of aging, including stiffening of the arterial wall, decreased blood flow, and so on. Considering the blood flow directly influences the BOLD signal, the present data might reflect vascular issues in aged people. The data showed a negative BOLD change in the initial part of the event-related time course, which might be the "initial dip" (Heeger & Ress, 2002; Vanzetta & Grinvald, 1999; Malonek et al., 1997) caused by an increase in deoxyhemoglobin attributable to a brief uncoupling between blood flow and oxygen utilization; this has been reported in patients with arterial stenoses who exhibited larger initial dip in left primary motor cortex (Roc et al., 2006). Therefore, it might be possible that blood flow in the amygdala in aged people increased slowly, and did not catch up the oxygen consumption, which caused an early large negative BOLD signal. And if the increase of the blood flow ended earlier, the BOLD signal would drop earlier, resulting in their sharpened hemodynamic pattern. Nevertheless, considering that we found such a time course difference between age groups only in the amygdala, and not in other affective brain regions, the observed age-related changes in time course difference cannot be due solely to this vascular change with aging. Nonetheless, future studies should consider measuring participants' vascular stiffness and other systemic hemodynamic measurements (arterial pressure, pulse wave, etc.) and relating these to the functional data.

The second explanation for age-related changes in the hemodynamic time course of the amygdala is alteration of neurovascular coupling with age. Neurovascular coupling refers to the processes by which neural activity influences the hemodynamic properties of the surrounding

vasculature (cf. D'Esposito, Deouell, & Gazzaley, 2003). It is still unclear whether neurovascular coupling is altered with aging (see Fabiani & Gratton, 2004; Rosengarten, Aldinger, Spiller, & Kaps, 2003; Buckner et al., 2000). The fact that we did not find age-related differences in the shape of the time course other brain regions, however, suggests that changes in neurovascular coupling might not be the main source of the age-related differences observed in the current study. This issue should be addressed by future studies.

A third possible explanation for age-related changes in the hemodynamics of the amygdala time course is that other brain areas, such as medial posterior OFC and adjacent inferior frontal gyrus (IFGorb), are up-regulating or sustaining the neural response to novel images in younger individuals, such that brains of younger people appear to hold on to novel information longer than brains of older people. This regulatory hypothesis is plausible given that OFC–IFGorb areas are reciprocally connected with the amygdala (Milad & Rauch, 2007; Petrides, 2007; Rempel-Clower, 2007; Bachevalier & Loveland, 2006). A caudal sector of lateral OFC (Brodmann's areas 12 and 13) is mainly interconnected with the amygdala (Carmichael & Price, 1995; Barbas & De Olmos, 1990; Aggleton, Burton, & Passingham, 1980), midline thalamus, and temporal pole (Bachevalier & Loveland, 2006). This connection is very unique because the lateral OFC area receives projections from both the amygdala and the temporo-polar area, whereas the rest of prefrontal cortex appear to have fewer connections with the amygdala and temporal pole (Ghashghaei & Barbas, 2002). Posterior OFC has been known to be involved in novelty processing (Petrides, 2007), along with the prefrontal cortices (Mesulam, 1998). Taken together with the results of the present study, this system is altered in older people.

Whether changes in the amygdala time course are due to the vascular effects of aging, alterations of neurovascular coupling, or reduced amygdala regulation by other brain regions in the affective workspace, these findings are consistent with the "aging brain hypothesis" that improved affective stability in later adulthood is a by-product of biological decline including structural and functional degradation of the amygdala and other affect-sensitive brain areas (Scheibe & Carstensen, 2010; Cacioppo, Berntson, Bechara, Tranel, & Hawkley, 2008). This does not mean that older people lose their capacity to respond to affective salient (including novel) environmental conditions, but rather, that older brains do not show sustained processing in this regard.

Furthermore, our results suggest that a consideration of novelty might play a key role in understanding the affective changes that occur with age. Without the moderating influence of stimulus novelty, there were no age-related differences in amygdala activation for positive versus negative stimuli. By including novelty, however, we were able to observe that positive stimuli were perceived as more familiar (and therefore perhaps not as evocative) in older individuals. This is consistent with the recent observation that younger adults exhibited novelty memory bias for the positive items, whereas older adults did not, such that older adults experienced greater overall familiarity for positive items (Spaniol, Voss, & Grady, 2008). On the surface, this might appear inconsistent with earlier published report, but in fact, previous studies of age-related differences in amygdala responsivity have been inconsistent. Older individuals were observed to show increased amygdala responses to positive IAPS images (Mather et al., 2004), but other studies have shown the opposite (Addis, Leclerc, Muscatell, & Kensinger, 2010). Furthermore, positive facial expressions did not activate the amygdala in older individuals more than in young individuals (Gunning-Dixon et al., 2003; Iidaka et al., 2002).

Finally, our findings on the subjective experience of arousal point to potentially important age-related changes in the subjective salience of visual images. Novel pictures were more subjectively arousing for everyone, reflecting their increased salience, but older individuals found them less arousing than did younger individuals. In addition, older individuals found high arousal pictures less arousing when compared to younger individuals. These differences in subjective arousal very likely reflect age-related reductions in interoceptive information from the body. Older individuals are less interoceptively sensitive (e.g., Khalsa, Rudrauf, & Tranel, 2009), and have blunted physiological reactivity (Levenson, Carstensen, Friesen, & Ekman, 1991). In addition, they are less likely to use information from the body to make decisions under uncertainty (Denburg, Tranel, & Bechara, 2005). According to the concept of "maturational dualism" (Mendes, 2010), these age-related changes in sensory feedback from the body has consequences for age-related changes in subjective experience of affect. Given the amygdala's role in regulating autonomic response, the peakier time course of the amygdala activation in older individuals might be related to these autonomic changes, although this is a point for future research.

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Note

1. To clarify whether the effect of stimulus novelty on the BOLD response in the amygdala was mediated by subjective arousal, we conducted mediation analyses in the left and right amygdala with

stimulus novelty as an independent variable, amygdala BOLD response estimated by FIR analysis as a dependent variable, and subjective arousal rating in every event as a mediator. For the right and left amygdala, subjective arousal only partially mediated amygdala response (indirect effects were significant; $z = 7.000$, $p < .0001$ for the right, $z = 6.064$, $p < .0001$ for the left). Nonetheless, stimulus novelty continued to directly predict amygdala response ($z = 1.89$, $p = .058$ for the right, $z = 3.31$, $p = .0009$ for the left). These findings replicate those reported in Weierich et al. (2010), indicating that amygdala responses to novelty were not solely related to the arousing nature of the novel pictures. In addition, we computed a set of correlational analyses to examine whether differences in subjective arousal ratings (novel − familiar) were related to the differences in amygdala BOLD activity in novel (vs. familiar) contrasts. These findings indicated that the difference between subjective arousal in novelty (vs. familiar) and in the amygdala contrasts for novelty (vs. familiar) were related for positive pictures only. The young group showed a larger positive correlation between subjective rating difference scores and right amygdala contrast in response to positive pictures, and a larger negative correlation for neutral pictures, but the older group did not show that pattern. Specifics of the analyses are available from the first author upon request.

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7. 心身症

はじめに

心身症とは

「心身症」という言葉は，医療の領域のみならず，現代のストレス社会でのキーワードの一つとなっている．一般にマスコミなどを通じて流布している心身症のイメージは「こころの病（やまい）」といったものであろうが，日本心身医学会は1991年に「心身医学の新しい診療指針」をまとめており，心身症を「身体疾患の中で，その発症や経過に心理社会的な因子が密接に関与し，器質的ないし機能的障害が認められる病態をいう．ただし，神経症やうつ病など，他の精神障害に伴う身体症状は除外する」と規定している．すなわち，心身症とは，こころの病ではなく，何かの病名でもなく，さまざまな身体疾患の病態を説明する概念の一つである．

そのキーワードの一つは「心身相関」――つまり，身体疾患の発症や経過には心理・社会的要因が強く関係するということであり，身体のみならず心理・社会的要因をも含めた，文字通り「こころ（心）」と「からだ（身）」の両方を，その相互作用に着目しながら治療の対象として扱うことが必要である，ということを表している．たとえば，気管支喘息は，「こころの病」といったイメージからは一見かけ離れているが，代表的な心身症であり，心理・社会的要因がその疾患の発症・増悪に深くかかわっていることが知られている．**表1**は「心身医学的な配慮が特に必要な疾患（いわゆる心身症とその周辺疾患）」としてあげられているものであるが，非常に広範な身体症状を呈する疾患が心身症の枠組みでとらえられることがわかる．

Key words
心身医学（psychosomatic medicine）
心身医学とは，心身相関を軸に，こころとからだはつながっている，という統合的な観点から人間をとらえ，そのシステムを科学的に解明し，さらにその知見をもとに，心身両面から全人的に，心身症を含む医学の諸問題に対処する領域の総称である．

心身症の病態仮説

心身症の病態の多くにかかわっているメカニズムと考えられるのは，人体におけるストレス状態から，大脳辺縁系・視床を中心とした情動の変化がもたらされ，そこを起点として，自律神経，ホルモン，免疫系を介した身体症状の出現をもたらす，というものである．つまり，心理・社会的ストレスが，大脳辺縁系・視床への脳内ネットワークの機能的・器質的変容をもたらし，心身症を出現させたり，あるいは既存の症状を維持・増悪させると考えられる．ここで，大脳皮質，とりわけ前頭葉は，このネットワー

表 1　心身医学的な配慮が特に必要な疾患（いわゆる心身症とその周辺疾患）

呼吸器系	気管支喘息，過換気症候群，神経性咳嗽，慢性閉塞性肺疾患など
循環器系	本態性高血圧症，本態性低血圧症，起立性低血圧症，冠動脈疾患，一部の不整脈，神経循環無力症，Raynaud 病など
消化器系	胃・十二指腸潰瘍，急性胃粘膜病変，慢性胃炎，non-ulcer dyspepsia，過敏性腸症候群，潰瘍性大腸炎，胆道ジスキネジー，慢性肝炎，慢性膵炎，心因性嘔吐，反芻，ぴまん性食道痙攣，食道アカラシア，呑気症およびガス貯留症候群，発作性非ガス性腹部膨満症，神経性腹部緊満症など
内分泌・代謝系	神経性食欲不振症，過食症，pseudo-Bartter 症候群，愛情遮断性小人症，単純性肥満症，糖尿病，腎性糖尿，反応性低血糖症など
神経・筋肉系	筋収縮性頭痛，片頭痛，その他の慢性疼痛，痙性斜頸，書痙，自律神経失調症，めまい，冷え症，しびれ感，異常覚，運動麻痺，失立失歩，失声，味覚脱失，舌の異常運動，振戦，チック，舞踏病様運動，ジストニア，失神，痙攣など
小児科領域	気管支喘息，過換気症候群，憤怒痙攣，消化性潰瘍，過敏性腸症候群，反復性腹痛，神経性食欲不振症，過食症，周期性嘔吐症，呑気症，遺糞症，嘔吐，下痢，便秘，異食症，起立性調節障害，心悸亢進，情動性不整脈，神経性頻尿，夜尿症，遺尿症，頭痛，片頭痛，めまい，乗り物酔い，チック，心因性痙攣，意識障害，視力障害，聴力障害，運動麻痺，Basedow 病，糖尿病，愛情遮断性小人症，肥満症，アトピー性皮膚炎，慢性蕁麻疹，円形脱毛症，抜毛，夜尿症，吃音，心因性発熱など
皮膚科領域	蕁麻疹，アトピー性皮膚炎，円形脱毛症，汎発性脱毛症，多汗症，接触皮膚炎，日光皮膚炎，湿疹，皮膚瘙痒症，血管神経性浮腫，尋常性白斑，扁平および尋常性疣贅など
外科領域	腹部手術後愁訴，頻回手術症，形成術後神経症など
整形外科領域	関節リウマチ，全身性筋痛症，結合織炎，腰痛症，背痛，多発関節痛，肩こり，頸腕症候群，外傷性頸部症候群，痛風，他の慢性疼痛性疾患など
泌尿・生殖器系	夜尿症，遺尿症，神経性頻尿，心因性閉尿，遊走腎，心因性インポテンス，前立腺症，尿道症候群など
産婦人科領域	更年期障害，機能性子宮出血，婦人自律神経失調症，術後不定愁訴，月経痛，月経前症候群，月経異常，続発性無月経，卵巣欠落症候群，卵巣機能低下，老人性膣炎，慢性付属器炎，痙攣性パラメトロパシー，骨盤うっ血，不妊症，外陰潰瘍，外陰瘙痒症，性交痛，性交不能，膣痛，外陰部痛，外陰部異常感，帯下，不感症，膣痙攣，流産，早産，妊娠悪阻，微弱陣痛，過強陣痛，産痛，軟産道強靱，乳汁分泌不全，マタニティーブルーなど
眼科領域	中心性漿液性脈絡網膜症，原発性緑内障，眼精疲労，本態性眼瞼痙攣，視力低下，視野狭窄，飛蚊症，眼痛など
耳鼻咽喉科領域	耳鳴，眩暈症，心因性難聴，アレルギー性鼻炎，慢性副鼻腔炎，嗅覚障害，頭重，頭痛，口内炎，咽喉頭異常感，嗄声，心因性失声症，吃音など
歯科・口腔外科領域	顎関節症，牙関緊急症，口腔乾燥症，三叉神経痛，舌咽神経痛，ある種の口内炎，突発性舌痛症，義歯不適応症，補綴後神経症，口腔・咽頭過敏症，頻回手術症など

（日本心身医学会教育研修委員会（編）．心身医学 1991；31：537-576）

クに介在し，心身症の病態に重要な役割を担っていることがわかってきている．つまり，心身症に重要な前頭葉機能としては，辺縁系あるいは視床と密接な関連をもちながら，ストレスによって引き起こされる情動のコントロールにかかわる領域群の働きが考えられている．

心身症と脳科学

ニューロイメージング技術の発達に伴って，PET や脳波などの脳機能を反映する測定が広く行われるようになった．特に 1992 年に機能的 MRI

(fMRI)がヒトの脳機能を非侵襲的に測定できることが発表されてからは，短期間のうちに数え切れないほどの報告がなされるようになった．心身医学研究についていえば，従来難しかったヒトでの身体と脳との関連――特に自律神経系，内分泌系，または免疫系などの末梢の指標と，脳との関連も探ることができるようになった．また，さまざまに工夫された心理課題などにより脳機能を測定することによって，動物実験では難しい「社会性」にまつわる脳機能画像研究なども行われるようになり，社会神経科学（social neuroscience）という分野も最近では脚光を浴びている．

この，心身医学における社会性の問題も興味深い．たとえば，神経学者Antonio R. Damasioらは，辺縁系損傷患者や，前頭前野のなかで感情を処理する部位に損傷があると，日常的な意思決定すらできないことを発見した．つまり，感情をなくせば理性的な意思決定ができるのではなく，逆に感情は意思決定に重要な影響を与えており，心身の問題は，そのまま社会性の問題でもあり，やはりそこにも前頭葉が深くかかわっている．

以下では，これまで心身医学領域で脳科学的なアプローチが行われてきたものから，いくつかトピックになってきたものを取り上げてレビューし，最終的に前頭葉がどのような役割を果たしているのかまとめてみたい．なお，気分障害*1，PTSD*2，パニック障害*3などにおいても興味ある知見があるが，他項に譲りたい．

＊1
本巻「気分障害」(p.112)参照．

＊2
本巻「PTSD」(p.120)参照．

＊3
本巻「パニック障害」(p.141)参照．

心身症と前頭葉

心血管系疾患と脳機能

心血管系動態と脳機能の関連については，脳が自律神経系のコントロールを介して末梢の生理動態を制御する系として，最もよく研究されているものの一つである．脳機能画像研究により，情動に関連した心血管系の変化は，交感神経・副交感神経系を介して扁桃体の活動と関連しており，心臓の収縮性は，不安による扁桃体の活動によって予見されるとする報告がある[1]．さらに大脳皮質のレベルでもその自律神経系の活動は調節されており，特に腹側の前頭葉領域（前部帯状回膝周囲〈perigenual anterior cingulate cortex：pACC〉および内側眼窩前頭野）は，副交感神経活動を反映する心拍変動と相関することが知られている．このpACCは組織学的には，より尾側の膝上部（caudal ACC：cACC）とより吻側の膝下部（subgenual ACC：sACC）に分けられる（**図1**）[2]．哺乳類の研究から，sACCは扁桃体から投射を受け，内側の前頭前野とともに抑制的に働き，cACCからは扁桃体へ投射が返されるというフィードバックのサーキットが存在し，扁桃体の活動のコントロールにかかわっていると考えられている．最近の情動ストレス課題によるfMRI研究では，pACCのより背側の

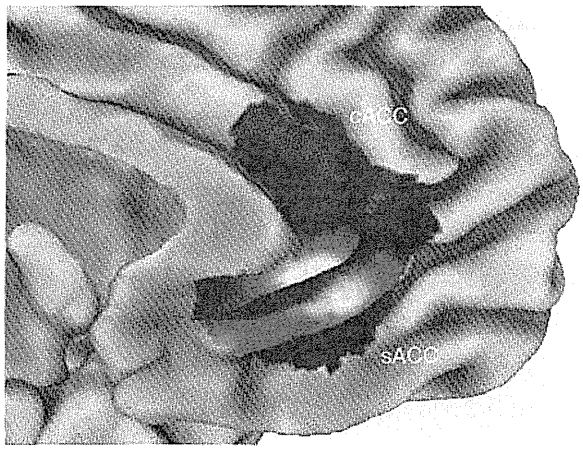

図 1　前部帯状回膝周囲（pACC）の扁桃体との機能的結合
赤は正の相関，青は負の相関を示す部位．
cACC：前部帯状回尾側膝上部，sACC：前部帯状回膝下部．
（Pezawas L. et al. *Nat Neurosci* 2005[2]）

前部帯状回（cACC）と扁桃体との機能的結合は，心血管系疾患の重要なリスクファクターである内頸動脈内膜中膜厚と相関することが報告されている[3]．この内側の前頭葉近辺の領域は，自律神経系を介してストレス制御に重要な役割を担っており，この内側前頭前野・pACC－扁桃体のネットワークの機能的変容によってストレス制御の不全が起こり，心血管系疾患を引き起こす可能性が示唆される．このpACCを含むサーキットの異常は，心血管系疾患のきわめて大きい社会的リスクファクターである，パートナーや家族の死に遭遇した後の遺族の脳活動でも認められている[4]．

機能性腸過敏症と体性疼痛

過敏性腸症候群（irritable bowel syndrome：IBS）は，大腸（もしくは小腸）の運動および分泌機能の異常で起こる病気の総称で，検査を行っても炎症や潰瘍など目にみえる異常が認められないにもかかわらず，下痢や便秘，ガス過多による下腹部の張り，痛みなどの症状が起こる．人口の10人に1人，消化器科受診患者の半数ほどを占めるともいわれるほど多い疾患であるが，しばしば慢性化・難治化する疾患で適切な対処が難しく，心理社会的なストレスなどの関与が大きいことが知られ，心身医学的なアプローチが重要な疾患の一つである．

消化管は，独自の消化管ホルモンや自動能，そして独自の神経ネットワーク（enteric nervous system：ENS）といった自律的なシステムを有する臓器であることが知られているが，最近は脳と消化管の機能的関連（脳–腸相関）が注目を集め，特に上記のIBSおよびそれを含む類縁疾患群（functional gastrointestinal disorder：FGID）においてその研究意義がクローズアップされている．焦点の一つは，「内臓知覚過敏」という概念で，内臓を主とした内的感覚がどのように脳で処理されるのかということである．Damasioらが唱えたソマティックマーカー（somatic marker）仮説によれば，「情動」とは，ある状況に陥ったときに身体全体の状態を脳が

モニターすることにより生じ，人間の「理性」的な判断は，この「情動」を土台にしてなされる．このときの情動の土台になる身体の状態として，特にinternal milieuと呼ばれる細胞内のホメオスターシスの状態や，内臓の状態が，情動にストレートに反映するとされる．消化管は，そのなかの重要なファクターの一つと考えられ，脳-腸相関を介して特に情動状態に影響を与えていると思われる．

脳の構造的には，IBS患者では灰白質濃度が，内側前頭前野，腹外側前頭前野，後部頭頂葉といった広範な領域で減少しているとする報告がある[5]．また，腸管をバルーンで拡張したときの脳血流の検討では，健常群や器質的な腸の炎症性疾患（潰瘍性大腸炎）と比べても，背内側前頭前野から前部帯状回（ACC）の膝前部・膝下部にかけてと扁桃体などの情動関連領域が活性化していたのに対し，右の外側前頭葉や背側橋・中脳水道周囲灰白質など，内生的な痛みの抑制に重要なサーキットでは活動が減少していた[6]．IBS患者では，内臓感覚入力に対して，扁桃体などの情動系のネットワークの反応が亢進し，疼痛コントロールにかかわる外側前頭前野などのネットワークの機能不全がある可能性がある．

慢性疼痛

日常生活に支障をきたすような疼痛が，6か月以上続くような状態を慢性疼痛と称する．身体表現性疼痛障害（ICD-10）・疼痛性障害（DSM）と呼ばれるものでは，その痛みを引き起こしている器質的病理的変化があるとは限らず，精密検査によって器質的原因が明らかにならないことがきわめて多い．機能的な慢性疼痛には，線維筋痛症，持続性特発性顔面痛，非特異的腰痛などがある．こうした機能的慢性疼痛はきわめて多い*4疾患であるが，しばしば重篤化しQOLや生産性を著しく低下させる．ここでの「痛み」はより意識的・主観的な体験として考えられ，情動と知覚システムの双方によって影響されるものであり，当然脳内のメカニズムと身体感覚の関連についての解明が必要となり，機能画像などを用いて研究されてきた．

痛みの脳内でのプロセスには複数の領域がかかわっているが，最も重要であると思われるのがACCである．そのうち，背側の中部帯状回（mid cingulate cortex：MCC）は，痛み情報の統合にかかわっているとされ，線維筋痛症や非特異的腰痛の患者群では，外的な侵害刺激に対するMCCの反応の亢進が認められている．MCCは侵害受容ニューロンを有し，運動領域に直接に投射している．一方，pACCは高濃度のオピオイド受容体を有し，情動・自律神経関連領域への直接投射がある．つまり，MCC/pACCは，侵害刺激に対して情動反応を形成するうえでのkey regionであり，慢性疼痛が起こる際にも重要な役割を果たしていると考えられている．

＊4
報告によって異なるものの，一般人口の10～20％．

さらに，身体表現性障害の患者では，痛み刺激に対する腹内側・眼窩前頭前野の反応低下および海馬傍回，扁桃体，ACC などの反応亢進が認められている．慢性疼痛における多くの機能的脳画像研究で共通しているのは，前頭前野領域の機能低下と，情動・疼痛関連領域の反応亢進である．

また，近年 default mode network（DMN）と呼ばれる神経ネットワークが知られるようになった．これは，特に何も外的な課題を与えない状態でも，ある特定のネットワークでの脳活動と，領域間の機能的結合が脳内でみられるというもので，この DMN では，なんらかの外的な課題施行時には神経活動が抑制されることが知られるようになった．この DMN で通常みられる神経活動抑制が，慢性疼痛の患者では減少していることがわかっている[7]．

さらに，視床においては，疾患群で疼痛があるときは脳血流が低下し，さらに症状が改善すると血流も改善することが多くの PET 研究などで明らかになっている．これは，視床における脳梗塞などで慢性的な疼痛が認められる（視床痛）ことを考えれば，きわめて妥当なことと考えられる．

一つ興味深いのは，慢性疼痛の脳皮質の構造解析の研究では，灰白質の減少が，視床や，下行性に痛みの調節をする外側前頭前野で認められることである．多くの慢性疼痛（慢性頭痛，IBS，線維筋痛症）などで類似の研究が行われているが，詳細な領域の違いはあるが，おしなべて灰白質の減少が示されている．また，拡散テンソル画像における構造的結合の研究では，やはりトップダウンの疼痛処理経路の障害がみられている[*5]．

こうした所見は，慢性疼痛に伴ううつや不安，薬物，生活スタイルなど，疾病に伴う状態を反映しているにすぎない可能性があるものの，前頭葉を含む機能的・構造的変容は明らかに脳内に存在し，疼痛の調節にかかわる機構の障害を反映していると考えられる．

＊5
中脳水道周囲灰白質と，前頭葉や扁桃体を含む結合．

摂食障害

さまざまなストレス状態が摂食行動に影響を与え，極端な拒食，やせ，過食・嘔吐など非適応的な食行動や，極端な肥満恐怖などを引き起こす摂食障害においても，脳機能の測定が行われている．今最も注目されているのは，前頭葉–線条体を中心とした自己制御のネットワークの障害説である[8]．このネットワークは，大脳皮質–線条体–視床–大脳皮質ループのなかの一部であり，皮質と皮質下をダイレクトにつなぐ回路である．線条体のうち，背側線条体を介する経路は，① 補足運動野，② 前頭眼野，③ 背外側前頭前野との結合があり，腹（内）側線条体を介するものは④ 外側前頭眼窩野，⑤ ACC との結合を有する．背側線条体を介する経路は，刺激–反応の学習や習癖形成にかかわっており，腹側線条体を介する経路は，報酬・動機形成などにかかわっているとされる．こうしたネットワークのうち，前頭前野を介するループは，目的達成に必要な思考・行動を自己コ

ントロールする中心的な役割を果たしていると考えられている．

＊6
一気に，ふつうの人が食べるよりも明らかに多い食べ物をむちゃ食いする．

過食症は，自分でコントロールできない過食[*6]を繰り返す．さらに，体重の増加を防ぐために，自己誘発性嘔吐，下剤・利尿薬・浣腸またはその他の薬剤の誤った使用，絶食，または過剰な運動などの不適切な代償行動を繰り返すこともあり，また性格的には衝動性のコントロールが悪くなることが知られている．この過食症を対象にした研究で，Stroop 課題などの抑制的コントロールを必要とする課題において，前頭葉–線条体の脳活動の減少が認められている[9]．また，過食症においてセロトニン代謝の障害が前頭葉で認められ，これよって，満腹感を得ることができなくなり，過食症の増悪につながっているという考えもあり，実際に選択的セロトニン再取り込み阻害薬（SSRI）による治療はある一定の効果を示すこともある．また，腹側線条体と前頭眼窩野のネットワークは，食物の報酬的価値を評価することにかかわる報酬系サーキットであり，食事摂取はこのサーキットのドーパミン放出を促進させる役割をもつ．食事に嗜好性の高い行動傾向とこのドーパミン放出の関連が，ラットでもヒトでも確認されており，過食症でもこの系の問題がある可能性がある．

＊7
体重増加に対する恐怖など．

拒食症（神経性無食欲症）は，極度の低体重と体重増加に対する恐怖，やせていても自分の体重を過大に感じるなどの症状から成り，過食症と共通する表現型[*7]もある．拒食症においても，やはりこの報酬系のネットワークの障害が示唆されている．特に，快・不快のフィードバックに対して，健常の場合は快のみに対して報酬系が活動するのに対し，拒食症においては，不快の場合も同様に活動してしまうことが知られている[10]．拒食症においては，ドーパミンに関連した報酬系の反応性の異常により，食物の報酬的価値の低下などが起こっている可能性がある．

気管支喘息

気管支喘息は，発作性の呼吸困難，喘鳴，咳を繰り返す疾患で，慢性的な炎症が気道に起こり，気道の過敏性が亢進することがその原因と考えられている．抗原の吸入，運動，感染などが喘息発作の引き金になるが，重要なことは，ストレスなどの情動状態の変化も発作の引き金になることであり，代表的な心身症として位置づけられている．

気管支喘息を対象にした機能画像研究も行われ，情動処理とのかかわりが検討されている[11]．被験者はあらかじめ個々人に特有の，発作を誘発させる抗原を吸入するチャレンジテストを行い，その後に初期（1時間後）および遅発（4時間後）の炎症反応が起こっているときに fMRI の施行を受けた．fMRI では，喘息にかかわる単語（例：「発作」）やネガティブな単語（例：「孤独」），また情動的に中性の単語（コントロール刺激）などが呈示され，それに対する脳活動が測定された．その結果，炎症後期において，内側前頭前野に近接した ACC（Brodmann 32 野）の脳活動が，喀