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ORIGINAL ARTICLE

CREB1 Genotype Modulates Adaptive Reward-Based Decisions in Humans

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Abstract

Cyclic AMP response element-binding protein (CREB) contributes to adaptation of mesocorticolimbic networks by modulating activity-regulated transcription and plasticity in neurons. Activity or expression changes of CREB in the nucleus accumbens (NAc) and orbital frontal cortex (OFC) interact with behavioral changes during reward-motivated learning. However, these findings from animal models have not been evaluated in humans. We tested whether CREB1 genotypes affect reward-motivated decisions and related brain activation, using BOLD fMRI in 224 young and healthy participants. More specifically, participants needed to adapt their decision to either pursue or resist immediate rewards to optimize the reward outcome. We found significant CREB1 genotype effects on choices to pursue increases of the reward outcome and on BOLD signal in the NAc, OFC, insula cortex, cingulate gyrus, hippocampus, amygdala, and precuneus during these decisions in comparison with those decisions avoiding total reward loss. Our results suggest that CREB1 genotype effects in these regions could contribute to individual differences in reward- and associative memory-based decision-making.

Key words: CREB1, decision-making, fMRI, genetics, reward

Introduction

Adaptive decision-making or goal action coordination is crucial for optimizing outcomes from interactions with complex environments. It relies on cognitive control to monitor decision-relevant conditions to select the response with the highest value, based on present conditions, rules/goal representation, and motivation (Leotti et al. 2010; Lee et al. 2012). People differ in their decision-making efficiency due to the influence of genetic and environmental effects on the cognitive processes involved in decision-making. We were interested in investigating the influence of individual differences in reward sensitivity and self-control on decisions of young and healthy humans. For this purpose, we conducted a functional MRI experiment to compare decisions associated with different reward outcomes and stimulus–response contingencies at the behavioral and neural network level. More specifically, participants could optimize the reward outcome if they adapted their decision to either increase or not to lose the delayed fixed reward by pursuing or

resisting immediate rewards. Our results from the behavioral analysis suggest that decision accuracy of participants was lower and more variable when pursuing a reward increase than when avoiding reward loss. This finding suggests individual differences in reward size-sensitive decisions and motivated us to test genetic variation that could contribute to such differences.

We focused on the gene encoding the cyclic AMP response element-binding protein (CREB). CREB plays a key role in the synaptic activity-dependent regulation of transcription-based neuroadaptations (Chawla and Bading 2001; Wolf and Linden 2012). These are induced by the processing of experiences to adapt neural systems and behaviors involved in reward-associated learning and memory (Hyman et al. 2006). More concretely, relations have been found between reward- or associative learning-related behaviors and the neuronal activation and/or expression of CREB in regions such as the amygdala (David et al. 2004; Viosca, Lopez de Armentia, et al. 2009), hippocampus (Kobayashi et al. 2005; Viosca, Malleret, et al. 2009; Suzuki et al. 2011; Shi et al. 2013), cingulate cortex (Walters et al. 2005; Narita et al. 2010), insula (Wei et al. 2002), orbital frontal cortex (OFC; Sun et al. 2010), and NAc (Barrot et al. 2002; Green et al. 2006; Dinieri et al. 2009; Shiflett et al. 2009; Muschamp et al. 2011). These brain regions contain CREB1 activity-sensitive neurons (Wei et al. 2002; Bermudez-Rattoni 2004; Dong et al. 2006; Bitner et al. 2007; Han et al. 2007; Wu et al. 2008; Mamiya et al. 2009; Shiflett et al. 2009; Zhou et al. 2009; Sun et al. 2010; Suzuki et al. 2011) and their activity contributes to the neural networks related to adaptive reward-based decision-making (Diekhof and Gruber 2010; Liu et al. 2011; Diekhof, Kaps, et al. 2012; Diekhof, Keil, et al. 2012). Moreover, in the NAc, the level of CREB expression and BOLD response has been related to that of neuronal activity as well as reward sensitivity (Dong et al. 2006; Green et al. 2006; Dinieri et al. 2009; Shiflett et al. 2009). These findings from animal models emphasize that CREB acts as a molecular regulator of plasticity in brain regions critical for reward-based behavior. In humans, single-nucleotide polymorphisms (SNPs) of *CREB1*, or near *CREB1* sequence, have been associated with *CREB1* mRNA expression in the brain, motivation-related traits (Lazary et al. 2011; Nishizawa et al. 2014), BOLD response in the insula (Perlis et al. 2008) or middle cingulate gyrus, precuneus, and temporal gyrus during emotion processing, and hippocampus function during memory recall (Juhasz et al. 2011; Li et al. 2014). Also, neuropsychiatric and neurodegenerative disorders that are characterized by dysfunction of motivation, emotion, or memory, such as addiction, bipolar disorder, suicide, and Alzheimer's disease, have been related to variations in the *CREB* gene, its expression, and CREB activation (Dowlatshahi et al. 1998; Yamamoto-Sasaki et al. 1999; Dwivedi et al. 2003; Robison and Nestler 2011; Li et al. 2012, 2014). It is therefore important to further elucidate the role of CREB1 in motivation- and memory-based human behavior. However, the contribution of CREB to reward-based learning and the underlying function of mesocorticolimbic networks have not yet been evaluated in humans. Our study is the first to address the question of whether variation in the *CREB1* gene contributes to individual differences in human adaptive reward-based decision-making at the behavioral and neural system level.

Materials and Methods

Participants

The study (protocol number 4/9/08) was approved by the ethics committee at the University Medical Center Göttingen. Participants were recruited from the University Göttingen and were paid 30€ that could be doubled depending on task performance. Prior to participation, volunteers gave written informed consent. Exclusion criteria were ethnicity other than Caucasian European, MRI contraindications, past or present psychiatric, neurological, or medical disorder, positive family history of psychiatric disorders, use of psychotropic drugs, drugs of abuse, being older than 31 or younger than 18, and having severe German language difficulties. All included participants were students at the Georg-August-University Göttingen aged between 19 and 31 years ($M = 24.01$, $SE = 0.16$). Imaging and performance data for at least 70% of all trials as well as *CREB1* genotypes were available from 224 participants for all SNPs, except rs2254137 ($N = 222$) and rs6785 ($N = 212$).

Genotyping

Human DNA was isolated from saliva collected into Oragene saliva DNA kits (DNA Genotek) using the Gentra Puregene Blood Kit (Qiagen) with standardized protocols. Genome-wide SNP genotyping was performed using Illumina OmniExpress Genotyping BeadChips according to the manufacturer's standard protocols and using 400 ng of DNA.

fMRI Task

Previous studies have used this (Trost et al. 2014) and similar versions (Diekhof and Gruber 2010; Diekhof, Keil, et al. 2012; Diekhof, Nerenberg, et al. 2012) of our event-related fMRI task (see Supplementary Fig. 1), to investigate how changes in stimulus–response-value contingency influence decision-making behavior and task-related BOLD signal in the brain.

Conditioning Training

One day before the experiment in the MRI scanner, participants were conditioned for reward-associated stimuli (red and green colored squares) by freely exploring the value (reward size) differences between responses (accepting/rejecting) to different stimuli. The stimulus–response-value contingencies are summarized in Supplementary Table 1a during conditioning.

Stimuli and Rewards

There were 30 Conditioned, 30 unconditioned none-cued, No-Target, and 60 unconditioned, cued Target stimuli trials for each task context (Reason and Desire). We used these task context labels because participants had to resist the desire to collect immediate rewards (reject the conditioned reward-associated stimuli) during Reason and were free to give into the desire to collect them during Desire. These 240 trials were distributed over 10 blocks of 4 and 8 trials each for each task context (Reason and Desire). The block trial number varied to reduce predictability of stimuli and hence expectation effects. Stimulus types occurred in pseudorandom order and were counterbalanced for order. Stimuli were presented in the center of the screen. Conditioned stimuli consisted of red and green colored squares. Squares of 6 other colors served as unconditioned Target stimuli if cued and unconditioned No-Target stimuli if not cued at the beginning of each block. The colors that served as cues changed every block. The task context changed every second block and was indicated at the beginning of each block. The delayed fixed reward consisted of 50 points and each of the immediate extra rewards consisted of 10 points. Final reward size depended on the points gained in each task block. Points were converted to money, paid to the participant at the end of the experiment.

Manipulation of Stimulus–Response-Value Contingencies During fMRI

After conditioning training, participants received instructions on decision rules and practiced the task, which they also briefly practiced and then executed in the scanner the next day. The response-value contingencies (see Supplementary Table 1b) differed now according to the stimulus type (Target and No-Target stimuli) for unconditioned stimuli and the task context (Reason/Desire) for Conditioned stimuli. Independent of the task context, it was correct to accept unconditioned stimuli if they were cued (Target) and otherwise to reject them (No-Target). Rejection of Conditioned stimuli was correct during the task context Reason. Acceptance of Conditioned stimuli was correct during the task context Desire. False responses irrespective of task context for unconditioned stimuli (Target and No-Target stimuli) and during the task context Reason for Conditioned stimuli or too slow responses reaction time (RT) >900 ms irrespective of stimulus would result in the complete reward loss for that block (loss of all points for that block) and start of a new block. During the task context Reason, participants gained a delayed fixed reward of 50 points at the end of a block only if decisions were accurate for all trials. During the task context Desire, acceptance of Conditioned stimuli gained 10 extra points per stimulus. Except for block aborts, immediate feedback followed each sample stimulus indicating 10 points for accepting a conditioned stimulus during the task context Desire and zero points for all other decisions. After block abort, the feedback was "goal failure." Therefore, extra points displayed during the immediate feedback served as immediate reward. All gained extra points were added to the delayed fixed reward of 50 points if achieved at the end of a block. At the end of a block, block point account was displayed. Although rejections of Conditioned stimuli during the task context Desire reduced only the extra but not the delayed fixed reward outcome at the end of a block, we counted such trials as incorrect during data analysis.

In summary, the value of accurate decisions (reward size) remained constant (avoid loss of delayed fixed reward) for unconditioned, but was context-dependent for Conditioned stimuli. During the task context Desire, participants could either continue to reject Conditioned stimuli, as required during the task context Reason to receive the delayed fixed reward, or adapt their decision and accept them to collect immediate extra rewards and thus increase the delayed reward. Accordingly, participants could choose whether or not to increase the delayed reward outcome by accepting or rejecting immediate extra rewards only for Conditioned stimuli during the Desire context. For all remaining task conditions, decisions would result either in loss or gain of the delayed fixed reward at the end of a task block.

Acquisition of Behavioral and fMRI Data

The task generation and behavioral data recording through the Presentation® Software (Neurobehavioral Systems, Albany, NY, USA) were co-triggered by the scanner impulse during the fMRI data acquisition. Stimuli were viewed through goggles (Resonance Technology, Northridge, CA, USA) and responses were indicated via a button press on a fiber optic computer response device (Current Designs, Inc., Philadelphia, PA, USA). Images were recorded on a 3-T whole-body scanner (Magnetom TRIO, Siemens Healthcare, Erlangen, Germany) with a standard 8-channel phased-array head coil. Three-dimensional blood oxygenation level-dependent (BOLD) contrast images were acquired by using a T_2*-weighted gradient-echo planar sequence [repetition time = 1900 ms; echo time = 33 ms; matrix size = 96 × 96; field of view = 192 mm; voxel size = 3 × 3 × 3.6 mm^3 (slice gap 0.6 mm); flip angle 70°; 31 axial slices; ascending order, 3 mm slice thickness, interslice gap = 0.6 mm]. During each of the 2 sessions, 185 volumes were obtained.

Statistical Analysis of Genetic and Behavioral Data

We used the SPSS software for Windows (IBM SPSS Statistics 21) for our statistical analysis of genetic and behavioral data. *CREB1* SNPs were selected as described in Supplementary Figure 2. The minor allele genotype was combined with the heterozygous genotype group to reduce the number of between-subject comparisons and analyzed as minor allele carrier models. Chi-squared tests were used to check Hardy–Weinberg equilibrium [α-level 0.05; 2 degrees of freedom (df)] and differences between genotype groups according to gender or handedness (α-level 0.05; 1 df). Independent sample *t*-tests [α-level 0.05; two-tailed; 222 df for all SNPs except rs2254137 (df = 220) and rs6785 (df = 210) because of missing genotype data] were used to analyze differences between genotype groups according to age. Bivariate Pearson's correlation coefficients (two-tailed) were used to test pair-wise linkage disequilibrium (LD) between SNPs. The cutoff for LD was set to an R^2 value of 0.7.

Decision accuracies were calculated from the number of correct trials divided by the number of all trials performed for each of the 6 task conditions (Conditioned, unconditioned Target, and No-Target stimuli during the Reason and Desire context) for each participant. Ratios of accurate trials and total number of trials performed were used to account for differences in the total trial number between task conditions and between participants that could occur through block aborts before the last trial. We tested for differences in accuracy between these 6 conditions using the non-parametric Friedman test because of significant ($P < 0.0001$) deviation from normality of accuracy for all conditions. Next, we conducted pair-wise comparisons between accuracy during the Reason and Desire task context for each stimulus type (Conditioned, Target, and No-Target) as well as between stimulus types separately for each task context (Reason and Desire) using the Wilcoxon test.

According to pair-wise LD analysis, only 4 *CREB1* SNP genotypes were not in high LD as defined as an R^2 of over 0.7. We tested whether these 4 *CREB1* SNP genotypes (combining minor allele homozygous with heterozygous genotype groups) showed significant effects on decision accuracy for Conditioned stimuli during Desire using Mann–Whitney *U* tests (two-tailed, Bonferroni-corrected significance level $\alpha = 0.0125$) using a minor allele carrier model.

Analysis of fMRI Data

Data analysis was performed using Statistical Parameter Mapping (SPM5; Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). Echo planar imaging (EPI) images were co-registered to the standard EPI image, realigned to correct for head motion, slice-time corrected, normalized into a common reference space (MNI), resampled at a voxel size of 3 × 3 × 3 mm^3, and smoothed (a 9-mm Gaussian kernel). The general linear model incorporated 11 predictors [6 task conditions for correct trials, 1 cue presentation, 1 immediate feedback, 2 feedback at the end of a block for each task context (Reason/Desire block), and 1 block abort]. The hemodynamic response was estimated for each of the 2 sessions, predictors, and subjects by convolving a delta function at stimulus onset with a canonical

hemodynamic response function. Resulting beta values for the task conditions No-Target Stimuli during Desire, Conditioned stimuli during the Desire and Reason context at each voxel, and for each subject were used to obtain 2 single-subject contrast images: "Conditioned stimuli during Desire minus Reason" and "Conditioned minus No-Target stimuli during Desire." Target stimuli trials were excluded from the image analysis, because they were twice as many compared with the conditioned or No-Target stimuli trials. At the group level analysis, we used these 2 single-subject contrast images including the covariates sex and age to generate one-sample *t*-test maps for each contrast. We used the "Conditioned stimuli during Desire minus Reason" contrast to identify the regional BOLD response related to reward size-sensitive compared with self-control-dependent decisions for reward-associated stimuli. The other contrast allowed us to compare reward-associated (Desire) with non-reward-associated stimuli (No-Target) for reward size-dependent (Desire) and -independent (No-Target) decisions.

Analysis of Genotype Effects on fMRI Data

We restricted our analysis of genotype effects on task contrasts that included the condition "Conditioned stimuli during Desire," because in our behavioral data analysis, only accuracy for this condition was significantly modulated by SNP rs10932201 genotype. These 2 single-subject contrast images grouped according to the genotype (61 subjects: genotype GG, 163 subjects: genotype AA/AG) were used as dependent variables to calculate 2 separate independent two-sample *t*-tests that included sex and age as covariates of no interest. This allowed us to compare GG versus AA/AG genotype carriers for the task contrast images "Conditioned stimuli during Desire minus Reason" and "Conditioned minus No-Target stimuli during Desire" at the whole-brain level. We used an uncorrected significance of $P < 0.001$ at the voxel-level combined with a cluster-level threshold corrected significance of $P < 0.05$ for the whole-brain analysis. We were particularly interested to test for rs10932201 *CREB* genotype effects in the cingulate cortex, OFC, insula, NAc, hippocampus, and amygdala based on their role in adaptive reward-based decision-making (Liu et al. 2011) and CREB activity-sensitive neurons (Hall et al. 2001; Wei et al. 2002; Dong et al. 2006; Shiflett et al. 2009; Zhou et al. 2009; Sun et al. 2010). For this purpose, we created one WFU-Pickatlas-based mask including all a priori regions of interest (ROIs). We applied this mask to our one-sample *t*-test maps for both task contrasts [using FWE small volume correction (SVC) $P < 0.0001$]. This allowed us to increase regional specificity of our analysis and identify the regional coordinates of significant, task contrast-specific effects on the BOLD response restricted to the volume of interest. Beta means were extracted from 10 mm spheres around these coordinates (see Supplementary Tables 7 and 8) for each participant and task contrast using the MarsBaR ROI toolbox for SPM (Brett et al. 2002). These beta means based on spheres around the coordinates identified for each task contrast were then tested for rs10932201 *CREB1* genotype effects using independent two-sample *t*-tests (two-tailed, α-level 0.05) in SPSS. We also used box plots to identify outliers of beta means and then tested how their exclusion would affect the results. We calculated FDR-adjusted *P*-values (two-tailed, α-level 0.05) to account for differences in the number of coordinates tested for each region using the *R*-3.1.0 software. MRIcron® software version 12/2012 (Chris Rorden, University of South Carolina, Columbia, SC, USA) was used to generate the brain maps shown in Figures 3, 4 and 5.

Results

Reward Sensitivity and Self-Control During Decision-Making

Decision accuracy was significantly different between task conditions ($\chi^2(5) = 439.04$, $P < 0.001$). Following up this finding, all 9 pair-wise comparisons (Fig. 1A) were significant according to Wilcoxon tests and a Bonferroni-corrected *P*-value of 0.006 to account for multiple testing.

Decision accuracy was higher during the task context Reason compared with Desire for all stimulus types. This difference was most pronounced between Conditioned stimuli (Fig. 1A), which is expected because task context changed only the stimulus–response-value contingency for Conditioned stimuli. Also for unconditioned Target and No-Target stimuli, decision accuracy was higher during the task context Reason compared with Desire, although the task context was irrelevant for their response value. These results suggest that our participants were able to resist the immediate rewards during Reason. Such high level of self-control during Reason presumably also supported decision accuracy for unconditioned stimuli.

Decision accuracy decreased from Conditioned to Target and No-Target stimuli during the Reason task context (Fig. 1A). The response value (avoid loss of the delayed fixed reward) was the

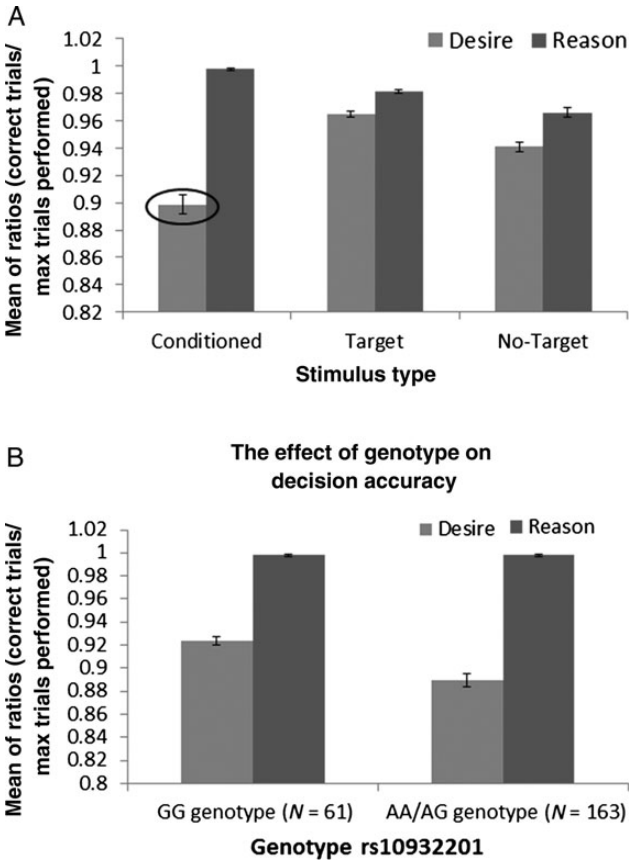

Figure 1 Decision-making behavior. (A) The effects of task context on decision accuracy for Conditioned, Target, and No-Target stimuli, and of stimulus type on decision accuracy during Reason and Desire. Between-subject variance was most pronounced for Conditioned stimuli during Desire. CREB1 genotype effects on reward size-sensitive decisions. (B) Significant effect of rs10932201 CREB1 genotype on decision accuracy for Conditioned stimuli during the task context Desire (exact significance, two-tailed: $P = 0.007$) but not during Reason (exact significance, two-tailed: $P = 0.394$). Error bars represent standard error of the mean.

same for all stimulus types during the Reason context. Therefore, the association with reward of conditioned but not unconditioned stimuli could explain higher accuracy for conditioned compared with unconditioned stimuli during Reason. The decreased accuracy for No-Target compared with Target stimuli suggests differences in the cognitive processing capacity between non-match and match-to-sample trials.

During the task context Desire, again participant's decision accuracy was better for Target than for No-Target stimuli, but reduced for Conditioned stimuli (Fig. 1A). This drop in decision accuracy for Conditioned stimuli during Desire likely results from insufficient motivation to gain extra rewards.

In comparison with all other task conditions, we found increased variance of decision accuracy for Conditioned stimuli during Desire likely due to individual differences in reward sensitivity/motivation. That such individual differences were largely absent for the remaining conditions is likely due to ceiling effects. This also means there was almost no variance in self-regulation that was needed to resist immediate rewards during Reason.

CREB1 SNP Genotypes

Allele frequencies for the 7 *CREB1* SNPs and the results for pairwise LD analysis are shown in Supplementary Tables 3a and b. All genotypes were distributed according to Hardy–Weinberg equilibrium. Participants in the genotype groups did not differ significantly with respect to age or gender (see Supplementary Table 4). We did not test whether genotype groups differed with respect to handedness due to cells with >20% expected frequency of <5.

CREB1 Genotype Effects on Reward Size-Sensitive Decisions

We considered decisions for Conditioned stimuli during Desire as reward size-sensitive because only then could participants increase the delayed reward outcome by collecting additional immediate rewards. We were interested to probe whether *CREB1* genotype effects contribute to the interindividual variability in decision accuracy that we observed for Conditioned stimuli during Desire. Only the less strongly linked *CREB1* SNP genotypes rs2253206, rs10932201, rs2254137, and rs2551928 were separately analyzed because of complete LD between rs2551928, rs1045780, rs6785, and rs2256941. During Desire, decision accuracy for Conditioned stimuli was significantly different between genotype groups for SNP rs10932201 at Bonferroni-corrected significance level $\alpha = 0.0125$. The results for all 4 SNPs are summarized in Table 1. Carriers of the GG compared with the AA/AG genotype showed higher decision accuracy for Conditioned stimuli during Desire (Fig. 1B). When we tested whether this *CREB1* genotype affects decision accuracy for Conditioned stimuli during the Reason context, the effect was not significant (Fig. 1B). We could not detect significant genotype effects on the accuracy for Conditioned stimuli during Reason. For this condition, performance was at ceiling, very homogeneous, less dependent on motivation or reward size sensitivity, and instead more dependent on self-regulation, suggesting a role of CREB in motivation or reward sensitivity but not in self-regulation.

Table 1 Results of the Mann–Whitney *U* tests (two-tailed, Bonferroni-corrected significance level $\alpha = 0.0125$) for the 4 relatively independent CREB1 SNP genotypes (combining minor allele homozygous with heterozygous genotype groups) tested on decision accuracy for "Conditioned stimuli during Desire"

CREB1 SNP	Median		*U*-value	*Z*-value	*P*-value	*r*
	Group 1	Group 2				
rs2253206	0.923	0.929	5235.00	−0.44	0.663	0.029
rs10932201	0.957	0.917	3806.50	−2.71	0.007	0.181
rs2254137	0.905	0.931	5124.00	−1.99	0.047	0.133
rs2551928	0.926	0.926	5522.50	−0.06	0.952	0.004

CREB1 Genotype Modulates Regional BOLD Response During Reward Size-Sensitive Decisions

We observed a significant ($P < 0.001$ uncorrected at voxel-level combined with cluster-level threshold correction $P < 0.05$) difference in the BOLD response related to decisions for "Conditioned stimuli during Desire minus Reason" between the GG compared with AA/AG genotype at the whole-brain level (Fig. 2A–D and see Supplementary Table 5). A significantly sized cluster was observed that included the left middle and posterior cingulate gyrus and the right precuneus. Compared with the AA/AG (163 subjects), the GG (61 subjects) genotype group showed an increased BOLD response. At the whole-brain level, no significant genotype effects were found on the BOLD response related to decisions for "Conditioned minus No-Target stimuli during Desire" ($P < 0.001$ uncorrected combined with cluster-level threshold correction all $P > 0.06$). The reversal of the genotype group contrast (AA/AG minus GG) for both task contrasts revealed no significant effect on the BOLD response at the whole-brain level (all $P > 0.001$ uncorrected).

Neural System Correlates for Self-control, Reward Size Sensitivity, and Reward Association-Dependent Decisions

We computed one-sample *t*-tests for whole-brain analysis ($P < 0.0001$, FWE-corrected) to reveal main clusters of positive or negative BOLD responses significantly correlated with our task contrasts (Fig. 3A,B and see Supplementary Table 6a–d). We observed significant effects on the BOLD response in the right inferior parietal, left middle frontal, and right insula cortex as well as on the reverse BOLD response in the postcentral gyrus bilateral and right superior occipital cortex for the task contrast "Conditioned stimuli Desire minus Reason." This contrast reflects the difference in the BOLD response between reward size sensitivity and self-control-dependent decisions while controlling for reward association/conditioning. Significant effects of the task contrast "Conditioned minus No-Target stimuli during Desire" on the BOLD response within main clusters were found in the left medial superior frontal and inferior parietal, right inferior occipital, and insula cortex as well as in the left middle cingulate gyrus and thalamus, right caudate nucleus, and parahippocampal gyrus, and also in the pons. Significant effects of this task contrast on the reversed BOLD response were observed in the right superior frontal and left superior motor cortex, left precentral gyrus, and right cerebellum. This contrast reveals differences in the BOLD response between decisions that were either dependent or independent of reward size sensitivity and reward association, while working memory load or demand for executive control was comparable.

Decision Contrast-Specific BOLD Response Within A Priori Mask of Regions

Owing to the large size of clusters obtained with the whole-brain mapping, we sought to increase regional specificity by using an SVC mask-based approach. When applying a WFU-Pickatlas-based mask including cingulate cortex, OFC, insula, NAc,

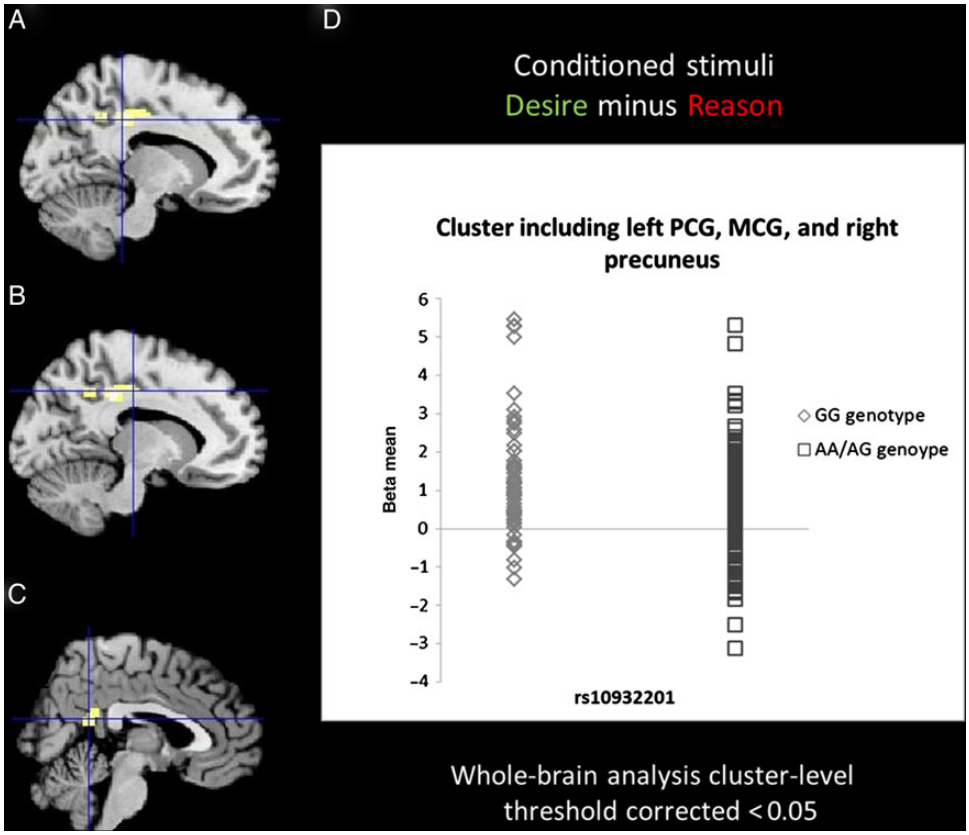

Figure 2 *CREB1* genotype influences on whole-brain regional BOLD response. rs10932201 *CREB1* genotype effect (GG minus AA/AG) on beta mean related to task contrast "Conditioned stimuli during Desire minus Reason" localized in the left posterior cingulate gyrus (*A*), middle cingulate gyrus (*B*), and right precuneus (*C*). Plot (*D*) depicts beta means at the cluster for each genotype group for the "Conditioned stimuli during Desire minus Reason" contrast (see also Supplementary Table 5).

hippocampus, and amygdala as a priori ROIs, we observed significant effects of both task contrasts on the BOLD response (FWE-corrected $P < 0.0001$) in all of these regions (Figs 4A and 5A, and see Supplementary Tables 7 and 8). Both task contrasts showed no significant effects on the reversed BOLD response (FWE-corrected $P < 0.0001$) in any of the a priori ROIs.

CREB1 Genotype Effects on BOLD Response in A Priori ROIs During Reward Size-Sensitive Decisions

We found that the BOLD response in the middle cingulate gyrus and the right and left posterior cingulate gyrus was significantly (two-tailed, α-level 0.05) increased in GG compared with AA/AG genotype carriers for the task contrast "Conditioned stimuli during Desire minus Reason" (Fig. 4B and see Supplementary Table 7). BOLD response in the middle cingulate gyrus, bilateral orbital frontal cortex, amygdala, hippocampus, and insula of the left hemisphere and the right NAc was significantly (two-tailed, α-level 0.05) increased in GG compared with AA/AG genotype carriers for the task contrast "Conditioned minus No-Target stimuli during Desire" (Fig. 5B,C and see Supplementary Table 8). Results are presented after the removal of outliers [outlier numbers: left OFC—2, hippocampus (−21 −33 −6)—2, hippocampus (−24 −30 −9)—3, and left MCG—1), although their effects on significance were minor.

Discussion

Our findings provide the first evidence that *CREB1* genotype contributes to individual differences in humans when they adapt their decisions to increase the size of the reward outcome. We then identified how the *CREB1* genotype influences BOLD signal contrasts that were related to decisions adapted to pursue an increased compared with a fixed size of reward in brain regions such as the NAc, OFC, insula cortex, middle and posterior cingulate gyrus, hippocampus, amygdala, and precuneus. Moreover, we identified the pattern of regional brain BOLD response that underlies reward-based decision-making in an exceptionally large sample of human participants. Taken together, our findings suggest that, by modulating the function of these brain regions, the *CREB1* genotype contributes to personal reward size sensitivity and associative memory for reward-related stimuli, while persons adapt their decisions to increase the reward outcome.

CREB1 Genotype Modulates Reward-Based Decisions and Related Brain Function

We investigated the functional neural structures involved in the adaptation of reward-based decisions and how their function and related behavioral performance are modulated by interindividual genetic differences in *CREB1*.

Our behavioral results indicate a contribution of the *CREB1* SNP rs10932201 genotype to individual decisions, when choosing an immediate reward to increase the delayed reward outcome. We observed no differences between genotype groups when participants had to resist immediate rewards to avoid loss of the delayed reward. Therefore, although both groups avoided losing the delayed reward, one group was better than the other in increasing the delayed reward outcome.

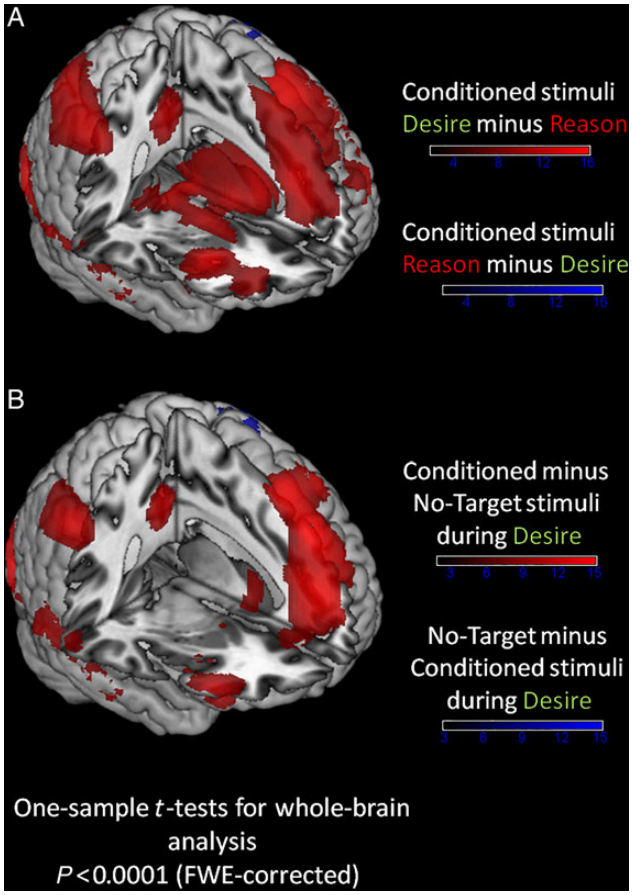

Figure 3 Decision contrast-specific neural system correlates. (*A*) BOLD response (red—t-value range) related to the task contrast "Conditioned stimuli during Desire minus Reason" with major clusters in the inferior parietal cortex and reverse BOLD response (blue—t-value range) in the postcentral gyri and superior occipital cortex (see also Supplementary Table 6a and b). (*B*) BOLD response (red—t-value range) related to the task contrast "Conditioned minus No-Target stimuli during Desire" with major clusters in the medial superior frontal, inferior parietal and occipital, middle occipital, middle cingulate and insula cortex, caudate nucleus, parahippocampal gyrus, pons and thalamus, and reverse BOLD response (blue—t-value range) with major clusters in the precentral gyrus, superior motor and frontal cortex, and cerebellum (see also Supplementary Table 6c and d).

We then used the "Conditioned stimuli during Desire minus Reason" contrast to compare the BOLD responses related to accurate decisions adapted to either pursue or resist immediate rewards to maximize the reward outcome. Conditioned stimuli during Desire and Reason were identical (same color), strongly related to reward (conditioning training), but differed with respect to the associated reward outcome (immediate extra vs. delayed fixed reward) and the accurate response (accept/reject). We found that the *CREB1* SNP rs10932201 genotype modulated the BOLD response in the precuneus and the middle and posterior cingulate gyrus related to this contrast at the whole-brain level. The posterior cingulate gyrus has been found to be engaged in various neural networks related to reward sensitivity and most consistently the representation of positive value (Liu et al. 2011). The BOLD response in the precuneus and middle cingulate cortex has also previously been associated with sensitivity of reward size or value (Liu et al. 2011; Jarcho et al. 2012). According to our results, these regions show a positive BOLD response for choices in the pursuit of increasing versus maintaining the delayed fixed reward outcome in the genotype group with more accurate decisions related to the immediate extra reward. The alternative of increased negative BOLD response in these regions related to maintenance versus increase of reward outcome appears less plausible. According to our behavioral analysis, genotype groups did not differ significantly when resisting the immediate to maintain the delayed fixed reward. Corresponding to our interpretation, *CREB1* genotype influenced modulation of these cortical regions enhances reward size sensitivity.

We then limited the search for significant task contrast-specific BOLD responses to a priori mask of regions, including cingulate gyrus, OFC, insula, hippocampal formation, amygdala, and NAc, using an SVC approach. We found that the BOLD response was significantly increased for Conditioned stimuli during Desire compared with these stimuli during Reason or No-Target stimuli in all regions. In neither contrast, did the reverse BOLD response reach our significance threshold. Our results thus support the role of these brain areas for decisions, while pursuing immediate rewards to increase the delayed reward as opposed to resisting them to maintain the delayed fixed reward.

Next, we tested whether mean BOLD response extracted from each of these a priori regions would be modulated by *CREB1* genotype effects. Analysis of the task contrast "Conditioned stimuli Desire minus Reason" again revealed an elevated BOLD response in GG compared with AA/AG genotype carriers in the middle cingulate, and left and right posterior cingulate cortex. Hence, our results of *CREB1* genotype effects on BOLD response related to this task contrast from the a priori regions are in agreement with the whole-brain analysis.

Although not detectable at the whole-brain level, we found that the *CREB1* genotype also modulated the BOLD response related to the other task contrast "Conditioned minus No-Target stimuli during Desire" in all a priori regions. Likewise for this task contrast, carriers of the GG compared with the AA/AG genotype showed an increased BOLD response in all regions. This task contrast compares the BOLD responses related to accurate decisions for conditioned and unconditioned stimuli during the task context Desire. These stimuli differed in their identity, because we used different colors that stayed the same for conditioned and changed for No-Target stimuli every block. Their relation to reward differed because only Conditioned stimuli were strongly associated with reward during conditioning training. They also differed because only the stimulus–response value for conditioned but not for No-Target stimuli changed with task context. The reward outcome (immediate extra vs. delayed fixed reward) and the accurate response (accept vs. reject) differed between these stimuli. Therefore, decisions for Conditioned more than No-Target stimuli depended on reward sensitivity to increase the reward outcome. Associative memory was engaged to recall the identity (24 h after conditioning) of reward-associated Conditioned but not unconditioned No-Target stimuli. Other memory-based and cognitive control processes involved in decision adaptation were more similar between Conditioned and No-Target stimuli. These include recalling of task context, respectively, 2 cues (for the duration of a block), updating of the value or the stimulus identity and corresponding adaptation of the response. Enhanced reliance on associative memory and reward sensitivity of decisions for Conditioned compared with No-Target stimuli may explain why we identified *CREB1* genotype effects on this contrast in the OFC, insula, cingulate gyrus, NAc, amygdala, and the hippocampus.

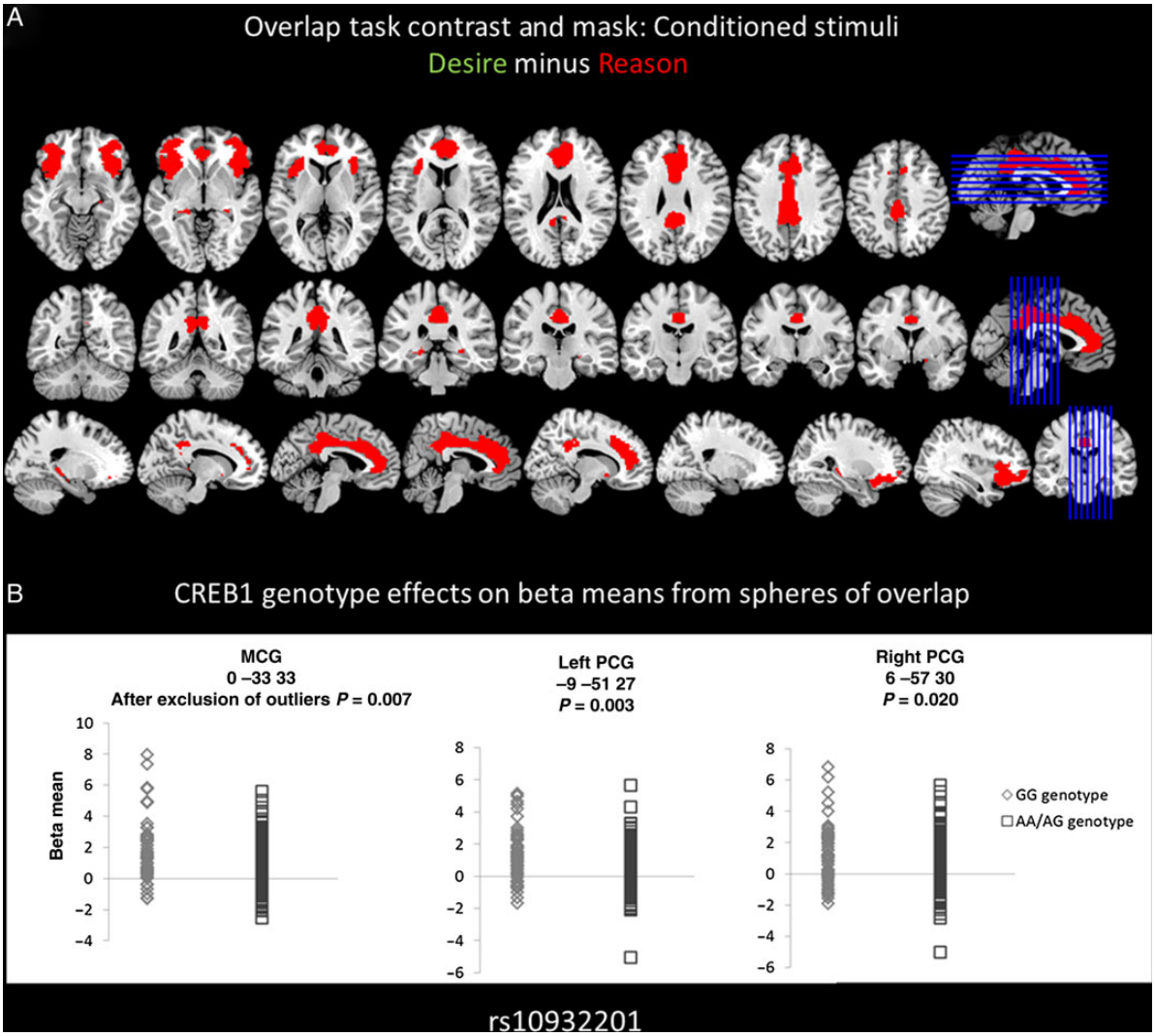

Figure 4 *CREB1* genotype effects on BOLD response for Conditioned stimuli during Desire minus Reason within a priori mask of regions. (*A*) Overlap between WFU-Pickatlas-based mask (blue) and BOLD response (red) related to the task contrast "Conditioned stimuli during Desire minus Reason." (*B*) GG, compared with AG/AA genotype, carriers show an increased beta mean related to the task contrast "Conditioned stimuli during Desire minus Reason" in mask-based regions (across the size of the sphere; see also Supplementary Table 7).

CREB-Dependent Adaptation of the Reward Response in Animal Models

Previous reports of CREB activation effects in regions representing a reward value or emotional salience, such as the OFC (Sun et al. 2010), insula (Wei et al. 2002), amygdala (David et al. 2004; Viosca, Lopez de Armentia, et al. 2009), and NAc (Barrot et al. 2002; Dong et al. 2006; Dinieri et al. 2009; Muschamp et al. 2011), suggest that in our study, *CREB1* genotype effects in these regions explain mainly individual differences in reward sensitivity. It has been shown that superior performance in reward-based decision-making, increased sensitivity to reward (Barrot et al. 2002; Dong et al. 2006; Dinieri et al. 2009; Muschamp et al. 2011) and decreased excitability of NAc neurons (Dong et al. 2006), correlated with decreased levels and activation of CREB in the NAc in various animal models. In addiction models, reduced drug sensitivity and increased drug self-administration have been linked to a CREB activity-mediated increase in NAc excitability (Barrot et al. 2002; Dong et al. 2006; Dinieri et al. 2009; Green et al. 2010). In line with these results, increased CREB levels in the OFC were shown to correlate with decreased cognitive control in rats performing a reward-based decision-making task (Sun et al. 2010). Higher CREB levels and activation in the PFC have been linked to cognitive performance deficits in rats, and this relationship showed a positive correlation with aging (Ramos et al. 2003). In addition, increases of CREB activation and protein level in the NAc have been reported during reward-associative learning (Shiflett et al. 2009; Pozzi et al. 2011) and CREB activation increased during changes of reward contingencies (Pozzi et al. 2011). These findings suggest that CREB activation serves as a signal to increase the behavioral responsiveness or sensitivity of an individual to emotionally salient cues or events (Nestler and Carlezon 2006; Shiflett et al. 2009). Perhaps, the CREB genotype associated with reward size-sensitive decisions in our study traces variation that modulates the magnitude of this CREB-based salience signal.

CREB1 Variants Affect Memory Function, Emotion, and Reward Processing in Humans

In humans, variation at a *CREB1* near locus has been associated with *CREB1* expression, reward dependence, drug sensitivity,

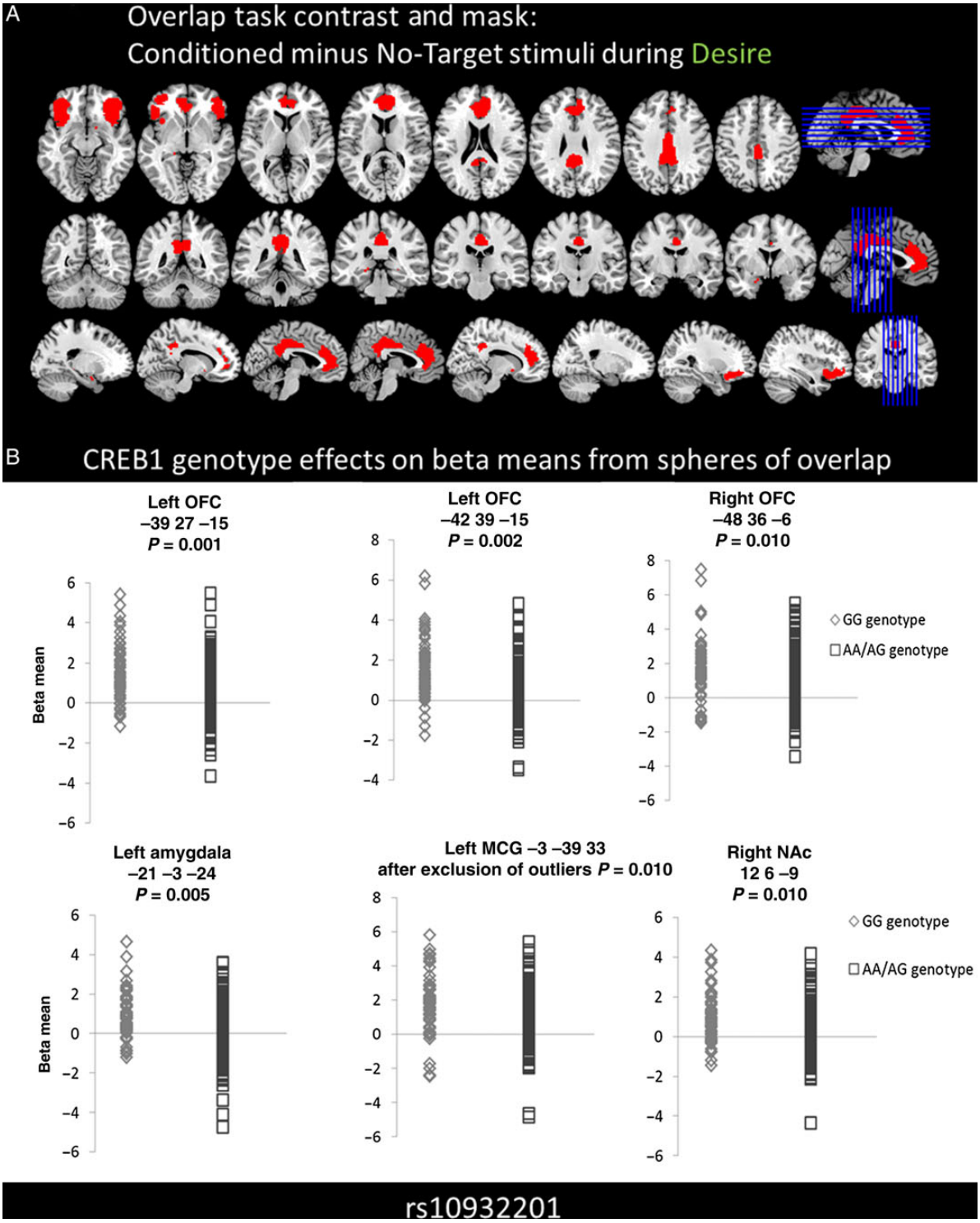

Figure 5 *CREB1* genotype effects on BOLD response for Conditioned minus No-Target stimuli during Desire within a priori mask of regions. (A) Overlap between WFU-Pickatlas-based mask (blue) and BOLD response (red) related to the task contrast "Conditioned minus No-Target stimuli during Desire." (B and C) GG, compared with AG/AA genotype, carriers show an increased beta mean related to the task contrast "Conditioned minus No-Target stimuli during Desire" in mask-based regions (across the size of the sphere; see also Supplementary Table 8).

and dependence (Nishizawa et al. 2014). Moreover, the *CREB1* SNP rs2253206 genotype has been linked with motivation-related personality traits like novelty seeking (Lazary et al. 2011). For this genotype, effects have also been shown on BOLD response during emotional face processing in the middle cingulate gyrus, precuneus, and temporal gyrus (Juhasz et al. 2011). SNP rs2253206, which lies close to and was in weak LD with our significant SNP rs10932201, showed no significant effect in our sample. Another *CREB1*-linked SNP genotype has been reported to influence BOLD response of the insula during emotion processing

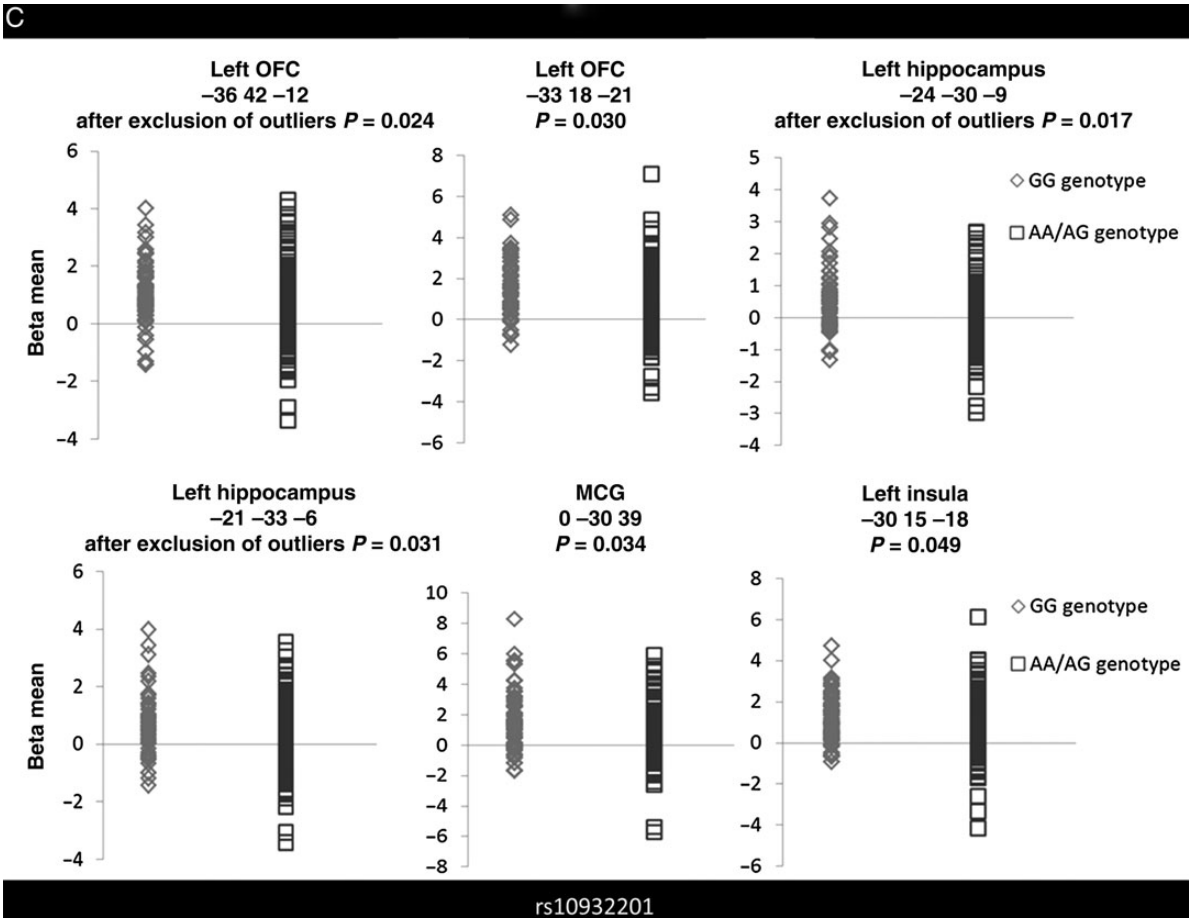

Figure 5 Continued

(Perlis et al. 2008). Interestingly, even if referring to variation at different loci, *CREB1* genotype effects on BOLD response related to reward as well as emotion processing were located in the insula, middle cingulate gyrus, and precuneus across these studies.

There is also evidence suggesting a link between a variant located upstream of *CREB1* and left hippocampus function during memory recall (Li et al. 2013). The variant significant in our sample has been related to a behavioral measure of memory retrieval in a Chinese sample of patients with major depression (Guo et al. 2014). We observed that this *CREB1* genotype modulated BOLD response in the left hippocampus for the task contrast "Conditioned minus No-Target stimuli during Desire." Because only Conditioned but not No-Target stimuli depended on associative memory, *CREB1* effects on BOLD response of this area are most likely memory-related. Our results link genetic variation in *CREB1* to individual differences in reward- and memory-based decision-making. Thereby, our study adds to the support for *CREB1* as potential susceptibility gene for disorders characterized by impaired reward processing, memory, and learning.

CREB1-Related Gene Expression in the Human Brain

Two *CREB1* SNPs rs2253206 and rs6785, investigated by us and others, have been shown to correlate with expression of *CREB1* or one of its target genes *BDNF* in the human hippocampus (Juhasz et al. 2011; Li et al. 2013). These 2 SNPs were weakly associated with our significant SNP. It is difficult to estimate expression effects because expression data are unavailable for most *CREB1* SNPs and most brain regions at present. We also investigated 3 SNPs located in the *CREB1* 3′ UTR that have been predicted to change the binding affinity of miRNAs (Li et al. 2013), potentially involved in the regulation of *CREB1* expression. These 3 SNPs were in complete LD in our sample, in weak LD with our significant SNP, and showed no significant effect on decision accuracy for Conditioned stimuli. Until we understand how these SNPs affect the expression of DNA and its derivatives in the human brain, our findings of associations between an SNP-based genotype, behavior, and brain function remain only suggestive. Above all, we only examined a small number of CREB-related SNPs and omitted interactions with other genes or environmental effects. The strength of our study is the convergence of findings based on analyses of behavioral performance and related neural correlates in a large sample of young and healthy humans. The significance of genotype effects varies across regions and contrasts. Most pronounced effects were found in the OFC for the contrast "Conditioned minus No-Target stimuli during Desire" and in the cingulate cortex for the contrast "Conditioned stimuli Desire minus Reason." After correcting for the number of tests carried out for each region, genotype effects remained significant for all regions except for the insula. Our findings should be viewed as preliminary until replicated.

In summary, our data from a large human sample, together with previous evidence, support the view that CREB1-associated mechanisms modulate brain function and behavior during

reward-based decision-making. These mechanisms could involve CREB-regulated genes and microRNAs such as c-Fos, Arc, BDNF, NGFI-A, dynorphin, miR-134, and miR-132 involved in the functional and structural adaptations of neurons (Wolf and Linden 2012). It would be interesting to see whether the *CREB1* genotype, associated with reward sensitivity, memory, and the BOLD response of specific brain regions in our sample, correlates with the expression of CREB targets in these areas.

Supplementary material

Supplementary material can be found at http://www.cercor.oxfordjournals.org/ online.

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References

Barrot M, Olivier JD, Perrotti LI, DiLeone RJ, Berton O, Eisch AJ, Impey S, Storm DR, Neve RL, Yin JC, et al. 2002. CREB activity in the nucleus accumbens shell controls gating of behavioral responses to emotional stimuli. Proc Natl Acad Sci USA. 99:11435–11440.

Bermudez-Rattoni F. 2004. Molecular mechanisms of taste-recognition memory. Nat Rev Neurosci. 5:209–217.

Bitner RS, Bunnelle WH, Anderson DJ, Briggs CA, Buccafusco J, Curzon P, Decker MW, Frost JM, Gronlien JH, Gubbins E, et al. 2007. Broad-spectrum efficacy across cognitive domains by alpha7 nicotinic acetylcholine receptor agonism correlates with activation of ERK1/2 and CREB phosphorylation pathways. J Neurosci. 27:10578–10587.

Brett M, Anton JL, Valbregue R, Poline JB. 8th International Conference on Functional Mapping of the Human Brain, June 2–6, Sendai, Japan. Available on CD-ROM in NeuroImage. 16. 2002. Region of interest analysis using an SPM toolbox [abstract].

Chawla S, Bading H. 2001. CREB/CBP and SRE-interacting transcriptional regulators are fast on-off switches: duration of calcium transients specifies the magnitude of transcriptional responses. J Neurochem. 79:849–858.

David JT, Cervantes MC, Trosky KA, Salinas JA, Delville Y. 2004. A neural network underlying individual differences in emotion and aggression in male golden hamsters. Neuroscience. 126:567–578.

Diekhof EK, Gruber O. 2010. When desire collides with reason: functional interactions between anteroventral prefrontal cortex and nucleus accumbens underlie the human ability to resist impulsive desires. J Neurosci. 30:1488–1493.

Diekhof EK, Kaps L, Falkai P, Gruber O. 2012. The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude—an activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. Neuropsychologia. 50:1252–1266.

Diekhof EK, Keil M, Obst KU, Henseler I, Dechent P, Falkai P, Gruber O. 2012. A functional neuroimaging study assessing gender differences in the neural mechanisms underlying the ability to resist impulsive desires. Brain Res. 1473:63–77.

Diekhof EK, Nerenberg L, Falkai P, Dechent P, Baudewig J, Gruber O. 2012. Impulsive personality and the ability to resist immediate reward: an fMRI study examining interindividual differences in the neural mechanisms underlying self-control. Hum Brain Mapp. 33:2768–2784.

Dinieri JA, Nemeth CL, Parsegian A, Carle T, Gurevich VV, Gurevich E, Neve RL, Nestler EJ, Carlezon WA Jr. 2009. Altered sensitivity to rewarding and aversive drugs in mice with inducible disruption of cAMP response element-binding protein function within the nucleus accumbens. J Neurosci. 29:1855–1859.

Dong Y, Green T, Saal D, Marie H, Neve R, Nestler EJ, Malenka RC. 2006. CREB modulates excitability of nucleus accumbens neurons. Nat Neurosci. 9:475–477.

Dowlatshahi D, MacQueen GM, Wang JF, Young LT. 1998. Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. Lancet. 352:1754–1755.

Dwivedi Y, Rao JS, Rizavi HS, Kotowski J, Conley RR, Roberts RC, Tamminga CA, Pandey GN. 2003. Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. Arch Gen Psychiatry. 60:273–282.

Green TA, Alibhai IN, Hommel JD, DiLeone RJ, Kumar A, Theobald DE, Neve RL, Nestler EJ. 2006. Induction of inducible cAMP early repressor expression in nucleus accumbens by stress or amphetamine increases behavioral responses to emotional stimuli. J Neurosci. 26:8235–8242.

Green TA, Alibhai IN, Roybal CN, Winstanley CA, Theobald DEH, Birnbaum SG, Graham AR, Unterberg S, Graham DL, Vialou V, et al. 2010. Environmental enrichment produces a behavioral phenotype mediated by low cyclic adenosine monophosphate response element binding (CREB) activity in the nucleus accumbens. Biol Psychiatry. 67:28–35.

Guo J, Liu Z, Dai H, Zhu Z, Wang H, Yang C, Xiao L, Huang Y, Wang G. 2014. Preliminary investigation of the influence of CREB1 gene polymorphisms on cognitive dysfunction in Chinese patients with major depression. Int J Neurosci. 124:22–29.

Hall J, Thomas KL, Everitt BJ. 2001. Fear memory retrieval induces CREB phosphorylation and Fos expression within the amygdala. Eur J Neurosci. 13:1453–1458.

Han JH, Kushner SA, Yiu AP, Cole CJ, Matynia A, Brown RA, Neve RL, Guzowski JF, Silva AJ, Josselyn SA. 2007. Neuronal competition and selection during memory formation. Science. 316:457–460.

Hyman SE, Malenka RC, Nestler EJ. 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci. 29:565–598.

Jarcho JM, Benson BE, Plate RC, Guyer AE, Detloff AM, Pine DS, Leibenluft E, Ernst M. 2012. Developmental effects of decision-making on sensitivity to reward: an fMRI study. Dev Cogn Neurosci. 2:437–447.

Juhasz G, Dunham JS, McKie S, Thomas E, Downey D, Chase D, Lloyd-Williams K, Toth ZG, Platt H, Mekli K, et al. 2011. The CREB1-BDNF-NTRK2 pathway in depression: multiple gene-cognition-environment interactions. Biol Psychiatry. 69:762–771.

Kobayashi M, Masaki T, Hori K, Masuo Y, Miyamoto M, Tsubokawa H, Noguchi H, Nomura M, Takamatsu K. 2005.

Hippocalcin-deficient mice display a defect in cAMP response element-binding protein activation associated with impaired spatial and associative memory. Neuroscience. 133:471–484.
Lazary J, Juhasz G, Anderson IM, Jacob CP, Nguyen TT, Lesch KP, Reif A, Deakin JF, Bagdy G. 2011. Epistatic interaction of CREB1 and KCNJ6 on rumination and negative emotionality. Eur Neuropsychopharmacol. 21:63–70.
Lee D, Seo H, Jung MW. 2012. Neural basis of reinforcement learning and decision making. Annu Rev Neurosci. 35:287–308.
Leotti LA, Iyengar SS, Ochsner KN. 2010. Born to choose: the origins and value of the need for control. Trends Cogn Sci. 14:457–463.
Li M, Luo XJ, Rietschel M, Lewis CM, Mattheisen M, Muller-Myhsok B, Jamain S, Leboyer M, Landen M, Thompson PM, et al. 2014. Allelic differences between Europeans and Chinese for CREB1 SNPs and their implications in gene expression regulation, hippocampal structure and function, and bipolar disorder susceptibility. Mol Psychiatry. 19:452–461.
Li Y, Shaw CA, Sheffer I, Sule N, Powell SZ, Dawson B, Zaidi SN, Bucasas KL, Lupski JR, Wilhelmsen KC, et al. 2012. Integrated copy number and gene expression analysis detects a CREB1 association with Alzheimer's disease. Transl Psychiatry. 2: e192.
Liu X, Hairston J, Schrier M, Fan J. 2011. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev. 35:1219–1236.
Mamiya N, Fukushima H, Suzuki A, Matsuyama Z, Homma S, Frankland PW, Kida S. 2009. Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory. J Neurosci. 29:402–413.
Muschamp JW, Van't Veer A, Parsegian A, Gallo MS, Chen M, Neve RL, Meloni EG, Carlezon WA Jr. 2011. Activation of CREB in the nucleus accumbens shell produces anhedonia and resistance to extinction of fear in rats. J Neurosci. 31:3095–3103.
Narita M, Matsushima Y, Niikura K, Takagi S, Nakahara K, Kurahashi K, Abe M, Saeki M, Asato M, Imai S, et al. 2010. Implication of dopaminergic projection from the ventral tegmental area to the anterior cingulate cortex in mu-opioid-induced place preference. Addict Biol. 15:434–447.
Nestler EJ, Carlezon WA Jr. 2006. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 59:1151–1159.
Nishizawa D, Fukuda K, Kasai S, Hasegawa J, Aoki Y, Nishi A, Saita N, Koukita Y, Nagashima M, Katoh R, et al. 2014. Genome-wide association study identifies a potent locus associated with human opioid sensitivity. Mol Psychiatry. 19:55–62.
Perlis RH, Holt DJ, Smoller JW, Blood AJ, Lee S, Kim BW, Lee MJ, Sun M, Makris N, Kennedy DK, et al. 2008. Association of a polymorphism near CREB1 with differential aversion processing in the insula of healthy participants. Arch Gen Psychiatry. 65:882–892.
Pozzi L, Sacchetti G, Agnoli L, Mainolfi P, Invernizzi RW, Carli M. 2011. Distinct changes in CREB phosphorylation in frontal cortex and striatum during contingent and non-contingent performance of a visual attention task. Front Behav Neurosci. 5:65.
Ramos BP, Birnbaum SG, Lindenmayer I, Newton SS, Duman RS, Arnsten AF. 2003. Dysregulation of protein kinase a signaling in the aged prefrontal cortex: new strategy for treating age-related cognitive decline. Neuron. 40:835–845.
Robison AJ, Nestler EJ. 2011. Transcriptional and epigenetic mechanisms of addiction. Nat Rev Neurosci. 12:623–637.
Shi Z, Chen L, Li S, Chen S, Sun X, Sun L, Li Y, Zeng J, He Y, Liu X. 2013. Chronic scopolamine-injection-induced cognitive deficit on reward-directed instrumental learning in rat is associated with CREB signaling activity in the cerebral cortex and dorsal hippocampus. Psychopharmacology (Berl). 230:245–260.
Shiflett MW, Mauna JC, Chipman AM, Peet E, Thiels E. 2009. Appetitive Pavlovian conditioned stimuli increase CREB phosphorylation in the nucleus accumbens. Neurobiol Learn Mem. 92:451–454.
Sun H, Green TA, Theobald DE, Birnbaum SG, Graham DL, Zeeb FD, Nestler EJ, Winstanley CA. 2010. Yohimbine increases impulsivity through activation of cAMP response element binding in the orbitofrontal cortex. Biol Psychiatry. 67:649–656.
Suzuki A, Fukushima H, Mukawa T, Toyoda H, Wu LJ, Zhao MG, Xu H, Shang Y, Endoh K, Iwamoto T, et al. 2011. Upregulation of CREB-mediated transcription enhances both short- and long-term memory. J Neurosci. 31:8786–8802.
Trost S, Diekhof EK, Zvonik K, Lewandowski M, Usher J, Keil M, Zilles D, Falkai P, Dechent P, Gruber O. 2014. Disturbed anterior prefrontal control of the mesolimbic reward system and increased impulsivity in bipolar disorder. Neuropsychopharmacology. 39:1914–1923.
Viosca J, Lopez de Armentia M, Jancic D, Barco A. 2009. Enhanced CREB-dependent gene expression increases the excitability of neurons in the basal amygdala and primes the consolidation of contextual and cued fear memory. Learn Mem. 16:193–197.
Viosca J, Malleret G, Bourtchouladze R, Benito E, Vronskava S, Kandel ER, Barco A. 2009. Chronic enhancement of CREB activity in the hippocampus interferes with the retrieval of spatial information. Learn Mem. 16:198–209.
Walters CL, Cleck JN, Kuo YC, Blendy JA. 2005. Mu-opioid receptor and CREB activation are required for nicotine reward. Neuron. 46:933–943.
Wei F, Qiu CS, Liauw J, Robinson DA, Ho N, Chatila T, Zhuo M. 2002. Calcium calmodulin-dependent protein kinase IV is required for fear memory. Nat Neurosci. 5:573–579.
Wolf C, Linden DE. 2012. Biological pathways to adaptability—interactions between genome, epigenome, nervous system and environment for adaptive behavior. Genes Brain Behav. 11:3–28.
Wu LJ, Zhang XH, Fukushima H, Zhang F, Wang H, Toyoda H, Li BM, Kida S, Zhuo M. 2008. Genetic enhancement of trace fear memory and cingulate potentiation in mice overexpressing Ca^{2+}/calmodulin-dependent protein kinase IV. Eur J Neurosci. 27:1923–1932.
Yamamoto-Sasaki M, Ozawa H, Saito T, Rosler M, Riederer P. 1999. Impaired phosphorylation of cyclic AMP response element binding protein in the hippocampus of dementia of the Alzheimer type. Brain Res. 824:300–303.
Zhou Y, Won J, Karlsson MG, Zhou M, Rogerson T, Balaji J, Neve R, Poirazi P, Silva AJ. 2009. CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. Nat Neurosci. 12:1438–1443.