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Structural and functional associations of the rostral anterior cingulate cortex with subjective happiness

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ABSTRACT

Happiness is one of the most fundamental human goals, which has led researchers to examine the source of individual happiness. Happiness has usually been discussed regarding two aspects (a temporary positive emotion and a trait-like long-term sense of being happy) that are interrelated; for example, individuals with a high level of trait-like subjective happiness tend to rate events as more pleasant. In this study, we hypothesized that the interaction between the two aspects of happiness could be explained by the interaction between structure and function in certain brain regions. Thus, we first assessed the association between gray matter density (GMD) of healthy participants and trait-like subjective happiness using voxel-based morphometry (VBM). Further, to assess the association between the GMD and brain function, we conducted functional magnetic resonance imaging (MRI) using the task of positive emotion induction (imagination of several emotional life events). VBM indicated that the subjective happiness was positively correlated with the GMD of the rostral anterior cingulate cortex (rACC). Functional MRI demonstrated that experimentally induced temporal happy feelings were positively correlated with subjective happiness level and rACC activity. The rACC response to positive events was also positively correlated with its GMD. These results provide convergent structural and functional evidence that the rACC is related to happiness and suggest that the interaction between structure and function in the rACC may explain the trait–state interaction in happiness.

1. Introduction

Since ancient times, people have thought about and desired happiness. Although happiness may be difficult to define scientifically, it has been defined to correspond to the sum of one's recent levels of positive affect, high life satisfaction, and infrequent negative affect (Diener, 1984, 1994; Diener et al., 1999). Because no appropriate device exists that can measure happiness objectively, researchers have generally relied on self-report measurements of happiness (i.e., subjective happiness level; Lyubomirsky and Lepper, 1999). Although subjective assessment of happiness has been shown to be associated with a wide variety of factors, including demographic status, personality traits, and circumstances (Lyubomirsky et al., 2005; Schimmack, 2008), subjective happiness appears to be trait-like and relatively stable over long periods of time (Lyubomirsky et al., 2005). In contrast, there is also a temporal aspect to happiness (hedonia; Diener, 1984, 1994; Diener et al., 1999). The temporal hedonic component of happiness is usually generated when we get the material objects and action opportunities we wish to possess or experience (Berridge and Kringelbach, 2011; Otake et al., 2006; Oyama, 2012; Schimmack, 2008; Seligman et al., 2005). Previous studies have demonstrated that individuals with high trait-like subjective happiness tend to evaluate their current emotional states more positively when they experience positive events (Matsunaga et al., 2011b; Schimmack, 2008). It also has been indicated that repetitive experiences of hedonic events elevate our subjective happiness level (Otake et al., 2006; Schimmack, 2008; Seligman et al., 2005). Two psychological models explain this interaction in happiness: a top-down and bottom-up model (Schimmack, 2008). The top-down model assumes that individuals with a positive propensity, such as optimism, evaluate their long-term happiness and temporal happy events more positively than others who experience a similar number of positive life events (Schimmack, 2008). In contrast, the bottom-up model suggests that consecutive hedonic experiences in each of the life domains (e.g., household income, housing conditions) elevate long-term happiness (Schimmack, 2008). Thus, the sum of positive life events may be important for constructing long-term happiness. However, previous

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epidemiological data could not indicate biological mechanisms underlying the interaction between the two aspects of happiness.

The biological mechanisms underlying trait–state interactions in happiness may be explicable by means of structural and functional interactions in certain brain regions. Numerous structural magnetic resonance imaging (MRI) studies have reported structural plasticity in the adult human brain (Driemeyer et al., 2008; Hamzei et al., 2012; Kwok et al., 2011). Gray matter is a major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and unmyelinated axons), glial cells (astroglia and oligodendrocytes), and capillaries; changes in gray matter reflect changes in cells or neuropil within the brain (Cook and Wellman, 2004; Wellman, 2001). Previous structural MRI studies have demonstrated associations between gray matter density (GMD), personality, and higher cognitive functions, including perception, intelligence, and memory (Giménez et al., 2004; Kanai et al., 2012; Kanai and Rees, 2011; Mårtensson et al., 2012; Spampinato et al., 2009). For example, lonely individuals show a reduction in gray matter in the left posterior superior temporal sulcus (pSTS), an area implicated in basic social perception (Kanai et al., 2012). Further, the GMD of the rostral anterior cingulate cortex (rACC) is reduced in patients with depression compared to healthy individuals (Du et al., 2012). Sharot et al. (2007) have previously suggested an association between gray matter reduction in the rACC in patients with depression and difficulties in creating detailed images of future events. Individual differences in human behavior and cognition may be explicable in terms of brain anatomy because greater cortical volume, or greater GMD, is associated with greater computational efficacy (Kanai and Rees, 2011). Therefore, if trait-like subjective happiness is represented in the structure of certain brain regions, and temporal happy feelings are represented by the activation of similar brain regions, the interaction between structure and function may be a key concept explaining the biological mechanisms underlying the interaction between the two aspects of happiness. This is because individuals with greater volumes of trait happiness-related brain regions may have higher-magnitude responses to positive stimuli and more easily experience happy feelings. This may be linked to the biological foundation of the top-down theory of happiness. Further, several structural MRI studies have reported training-related structural plasticity in the adult human brain (Driemeyer et al., 2008; Hamzei et al., 2012; Kwok et al., 2011). It has been demonstrated that motor skill training and a variety of trial and error learning increase GMD in cortical motor areas, which is also accompanied by performance improvements (Hamzei et al., 2012). Thus, repetitive stimulation of certain brain regions may increase their cortical volume, suggesting that continuous experiences of positive events might stimulate temporal happiness-related brain regions and enlarge the cortical volumes associated with trait happiness. This may be the biological foundation of the bottom-up theory of happiness.

However, the neural substrates of subjective happiness remain somewhat ambiguous. A recent structural MRI study demonstrated an association between gray matter volume in the insular cortex and subjectively assessed eudemonic well-being (Lewis et al., 2014). Eudemonia is one of the important trait-like aspects of happiness and corresponds to certain cognitive and/or moral aspects of a well-lived life (Berridge and Kringelbach, 2011). The insular cortex is associated with interoceptive awareness because it is the top-level center of the ascending pathways of information flow from the body to the brain (Craig, 2009). Because one of the concepts of happiness centers on positive inner feelings, such as pleasure and joy (Oishi et al., 2013), such an association between the interoception-related brain region and subjective happiness might make sense. Another structural MRI study indicated an association between subjective happiness and gray matter volume in the precuneus (Sato et al., 2015). When we evaluate our life events, there is no objective answer based on external circumstances; rather, the evaluation is based on our own experiences or preferences. A recent neuroimaging study indicated that various neural networks including the medial prefrontal cortex, precuneus, and the superior temporal gyrus are consistently activated by such subjective evaluation (Nakao et al., 2012). These neural networks are involved in episodic memory retrieval, theory of mind, and prospection, which is the act of thinking about the future (Buckner and Carroll, 2007; Krueger et al., 2009; Nakao et al., 2012; Northoff and Bermpohl, 2004; Roy et al., 2012). Thus, the association between the precuneus and subjective happiness also has face validity. However, a meta-analysis of neuroimaging studies—indicating the brain regions associated with happiness through a variety of psychological tasks, such as happy face recognition, listening to happy music, and recollection of happy memories, all of which can induce temporary states of happiness (Cerqueira et al., 2008; Damasio et al., 2000; Mitterschiffthaler et al., 2007; Sato et al., 2004)—confirmed that experimentally induced happiness consistently activates the superior temporal gyrus (STG; Brodmann area [BA] 22), rACC (BA 24), cerebellum, thalamus, lingual gyrus, inferior occipital gyrus, insular cortex, and basal ganglia (Vytal and Hamann, 2010). A different meta-analysis indicated that happiness consistently activates only the peristriate (Lindquist et al., 2012). In contrast, Berridge and Kringelbach (2011) advocated the importance of reward-related regions such as the nucleus accumbens and ventral pallidum in happiness processing. The lack of consistency between the neural correlates of trait-like subjective happiness and of temporal happy feelings is problematic, although it is possible that not just one cortical area is involved in happiness processing.

In the present study, in order to clarify the association between structure–function interactions in the brain and trait–state interactions in happiness, we conducted both voxel-based-morphometry (VBM, Experiment 1) and functional MRI using a task that induced happy feelings (Experiment 2). We first measured the GMD of 106 healthy Japanese participants using VBM. In Experiment 1, participants were asked to evaluate their subjective happiness level using the Japanese version of the Subjective Happiness Scale (JSHS; Matsunaga et al., 2011a, 2011b; Shimai et al., 2004). The JSHS is a four-item scale that measures relatively stable, trait-like subjective happiness. We searched for brain regions in which there were positive correlations between GMD and the JSHS score. Subsequently, to assess the association between the GMD and temporal happiness-related brain activations, we conducted Experiment 2, in which 26 healthy Japanese participants took part in an fMRI study. They were asked to imagine how happy they would feel when they encountered several types of emotional life events (positive, neutral, negative, and non-emotional), while images depicting each life event were presented (Fig. 1). The participants rated their present level of happiness subsequent to imagining each event by means of a visual analog scale (VAS). We assessed associations between blood oxygen level-dependent (BOLD) response and GMD. We revealed structural and functional associations of the rACC with subjective happiness by combining the results of Experiments 1 and 2.

2. Methods

2.1. Experiment 1

2.1.1. Participants

We recruited 106 right-handed healthy volunteers (49 men and 57 women; age range: 18–34 years; mean age: 21.4 years), following approval of the study by the Ethics Committee of the National Institute for Physiological Sciences. All participants provided written informed consent in accordance with the Declaration of Helsinki. Participants were excluded if they had any chronic and infectious illnesses, and if they had taken medication in the week prior to the experiment. Although we did not record the social status of all participants, almost all participants in Experiment 1 were Japanese undergraduate and graduate students of universities located near the National Institute for Physiological Sciences. We did not record the body mass index (BMI) in Experiment 1.

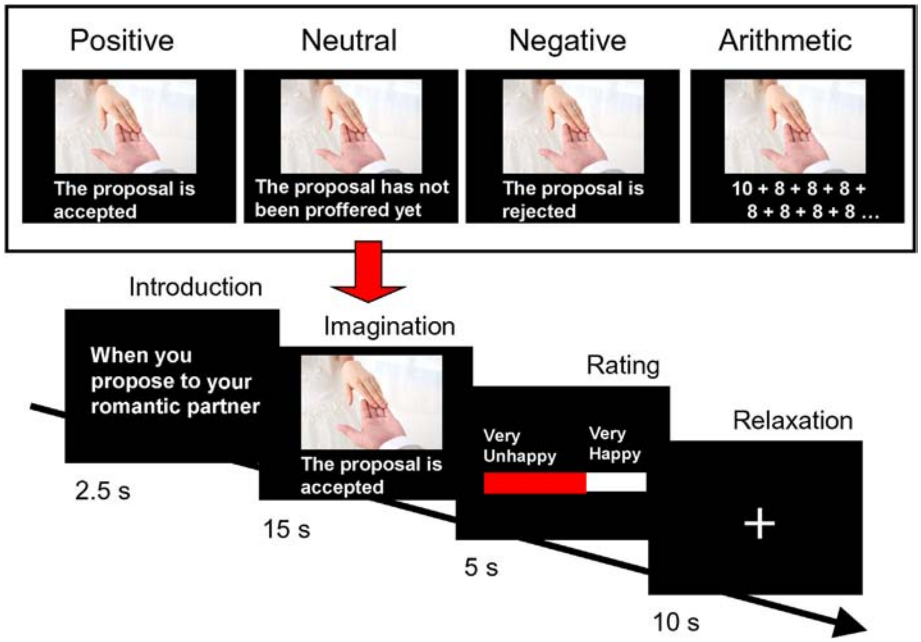

Fig. 1. Sequence of events in a trial. The example picture was actually used in the present functional MRI study. Statements were written in Japanese in the task.

2.1.2. Evaluation of subjective happiness level

To assess the subjective happiness level, participants completed the JSHS (Matsunaga et al., 2011a, 2011b; Shimai et al., 2004). The JSHS is the Japanese version of the Subjective Happiness Scale (SHS), developed by Lyubomirsky and Lepper (1999). The SHS exhibits excellent psychometric properties, such as high internal consistency, a unitary structure, and stability over time (Lyubomirsky and Lepper, 1999). Therefore, the SHS is a widely used psychometric tool to evaluate subjective happiness levels (Matsunaga et al., 2011a, 2011b; Shimai et al., 2004; Zhang et al., 2013). The JSHS subjectively assesses whether a person is happy or unhappy and assesses the person's positive personal trait. Thus, the JSHS assesses the cognitive evaluation about one's happiness level. Each item is answered on a 7-point Likert scale, and we asked the participants to circle the point on the scale that they feel is most appropriate in describing the following statements and/or questions: 1) “In general, I consider myself,” 1 (not a very happy person) to 7 (a very happy person). 2) “Compared to most of my peers, I consider myself,” 1 (less happy) to 7 (more happy). 3) “Some people are generally very happy. They enjoy life regardless of what is going on, getting the most out of everything. To what extent does this characterization describe you?” 1 (not at all) to 7 (a great deal). 4) “Some people are generally not very happy. Although they are not depressed, they never seem as happy as they might be. To what extent does this characterization describe you?” 1 (not at all) to 7 (a great deal). The internal consistency, test–retest reliability, and convergent discriminant validity of the JSHS have been confirmed previously (Lyubomirsky and Lepper, 1999; Matsunaga et al., 2011a, 2011b; Shimai et al., 2004). Cronbach's alpha for the JSHS was 0.82 in the original study of Shimai et al. (2004).

2.1.3. Voxel-based morphometry

A whole-brain, high-resolution T1-weighted anatomical magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) MRI was acquired for each subject using a 3-Tesla MRI scanner (Verio; Siemens Ltd., Erlangen, Germany). Anatomical brain images were processed using the VBM8 toolbox (r435; http://dbm.neuro.uni-jena.de/vbm/), which was incorporated into the Statistical Parametric Mapping (SPM) software (SPM8 revision 3684; The Wellcome Department of Cognitive Neurology, London, UK), and implemented via Matlab 2010a (MathWorks, Sherborn, MA, USA). VBM8 involves bias correction, tissue classification, and spatial normalization with diffeomorphic anatomical registration through exponentiated Lie algebra (Ashburner, 2007). We used the default parameters of VBM8. As a result, segmented, normalized, and modulated gray matter images were provided for subsequent VBM statistical analysis. The modulation process was performed using Jacobian determinants of the nonlinear deformations employed for normalization so that voxel intensities reflected regional gray matter volumes adjusted for individual brain sizes. Finally, the modulated gray matter images were smoothed with an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. After preprocessing of anatomical brain images, gray matter density in the whole brain was examined for potential correlations with subjective happiness level by using a multiple regression design. Age was considered a covariate of no interest to partial out its contribution to gray matter density. The statistical threshold was set at an uncorrected $p < 0.001$ at the voxel level and at $p < 0.05$, family-wise error (FWE) corrected, at the cluster level. The plot function in SPM8 was used to generate the scatter plot indicating the correlation between parameter estimates at [−6, 36, 1] and JSHS scores.

2.2. Experiment 2

2.2.1. Participants

Twenty-six right-handed healthy volunteers (11 men and 15 women; age range: 18–28 years; mean age: 21.9 years) took part in Experiment 2. Ethical approval and exclusion criteria were the same as those for Experiment 1. Twenty-five participants were Japanese undergraduate and graduate students of universities located near our institute; one participant was a Japanese office worker. The mean body mass index (BMI) of participants was 20.3 (range: 17.1–24.5), indicating that all were in the normal weight range. In addition, to assess the subjective happiness level of participants in Experiment 2, they completed the JSHS similar to Experiment 1 (Matsunaga et al., 2011a, 2011b; Shimai et al., 2004). Most participants from Experiment 1 participated in Experiment 2, but two participants from Experiment 2 did not participate in Experiment 1.

2.2.2. Experimental stimuli

We searched for life events that could induce happy feelings. Before the fMRI experiment, we asked 16 laboratory members (9 men and 7 women; age range: 22–46 years; mean age: 28.9 years), who did not participate in the fMRI experiment, to evaluate how happy they would feel in several life events in the questionnaire. Based on the evaluation scores in this questionnaire, we selected 12 positive life events, such as marriage, travel, and good family relationships (Table 1). We obtained copyright-free pictures indicating each life event from the Internet (http://www.photo-ac.com) and displayed the images in the center of the display.

The events had two components, namely, the occasion and the outcome. For example, "When you propose to your romantic partner (*occasion*), the proposal is accepted (*outcome*)." We then changed the outcomes to devise negative events ("the proposal is rejected") and neutral events ("a proposal has not been proffered yet"). In this manner, we created 12 positive, 12 negative, and 12 neutral events (Table 1). In addition, to both reduce the priming effects of emotional stimuli during functional MRI and add a low-level control (LLC), we devised 12 arithmetical conditions, consisting of 6 successive subtractions ($100 - 2 - 2 - 2 - 2 \ldots$, $100 - 3 - 3 - 3 - 3 \ldots$, $100 - 5 - 5 - 5 - 5 \ldots$, $100 - 6 - 6 - 6 - 6 \ldots$, $100 - 7 - 7 - 7 - 7 \ldots$, $100 - 8 - 8 - 8 - 8 \ldots$) and 6 successive additions ($10 + 2 + 2 + 2 + 2 \ldots$, $10 + 3 + 3 + 3 + 3 \ldots$, $10 + 5 + 5 + 5 + 5 \ldots$, $10 + 6 + 6 + 6 + 6 \ldots$, $10 + 7 + 7 + 7 + 7 \ldots$, $10 + 8 + 8 + 8 + 8 \ldots$). Participants were asked to perform the calculation while it was displayed. Thus, there were four conditions in total: positive, neutral, negative, and arithmetical (Fig. 1).

2.2.3. Experimental task and procedure for functional MRI

Participants were asked to perform the life event imagination task depicted in Fig. 1. Each trial commenced with presentation of a fixation cross for 30 s, followed by: 1) an introductory text phrase, explaining the life event (2.5 s); 2) the imagination phase (15 s); 3) a rating phase (5 s); and 4) a relaxation phase (10 s). During the imagination phase, a picture was presented along with a statement pertaining to the outcome (positive, neutral, or negative) or an arithmetical problem, and participants were asked to imagine how happy they would feel in this situation including the LLC condition. Following the picture presentation, participants were allowed 5 s to rate their current level of happiness using a VAS, specified at the 0% point of the scale ("very unhappy"), 50% point ("neither happy nor unhappy"), and 100% point ("very happy"). Subsequent to the rating, participants had a 10-s period of rest, during which they looked at a fixation cross before the onset of the next trial. The experiment consisted of 48 trials. Four functional imaging runs (12 trials, about 7 min in total) were performed for each subject, and the 12×4 conditions were presented randomly throughout the whole acquisition run. Participants received four training trials prior to the experiment to familiarize themselves with the procedure. The order of the four conditions was counterbalanced across participants.

2.2.4. Statistical analyses of behavioral data in the functional MRI paradigm

Behavioral results are expressed as means $\pm$ SEM. The rating scores for happiness in each condition were compared using repeated measures analysis of variance (ANOVA) followed by multiple comparisons test with Bonferroni correction.

2.2.5. Functional MRI data acquisition

Functional imaging was conducted using the 3-Tesla MRI scanner (Verio; Siemens Ltd., Erlangen, Germany). Each subject's head was immobilized within a 32-element phased-array head coil. The imaging was performed using an echo-planar imaging (EPI) gradient-echo sequence (echo time [TE] = 30 ms, repetition time [TR] = 2500 ms, field of view [FOV] = 192×192 mm^2, flip angle = 80°, matrix size = 64×64, 39 slices, slice thickness = 3 mm, total number of volumes = 168). A whole-brain, high-resolution T1-weighted anatomical MP-RAGE MRI was also acquired for each subject (TE = 1.98 ms, TR = 1800 ms, FOV = 256×256 mm^2, flip angle = 9°, matrix size = 256×256 pixels, and slice thickness = 1 mm).

Table 1
Hypothetical life events used in the functional MRI task (12 occasions and 12 positive, 12 neutral, and 12 negative outcomes). All statements were written in Japanese in the task.

Occasion	Outcome
When you feel hungry,	your stomach is full after eating delicious food. (positive)
	you think whether or not to cook. (neutral)
	you are ostracized by peers at a dinner party. (negative)
When you are at home,	you enjoy yourself with your family. (positive)
	you read the newspaper alone in your room. (neutral)
	you hear that your family had an accident. (negative)
When you sleep,	you lie down on a warm bed comfortably. (positive)
	you prepare the bed. (neutral)
	you can't sleep due to an intense headache. (negative)
When you go on a trip,	you go to various places and fully enjoy traveling. (positive)
	you make plans to travel. (neutral)
	you lose your passport and can't return to Japan. (negative)
When you are job hunting,	you get an informal invitation from the company you want to work for. (positive)
	you go to a job seminar. (neutral)
	you receive no informal invitation from any company. (negative)
When you go to the party in the Japanese style pub,	you enjoy yourself with your friends. (positive)
	you decide whether to sit down at the counter. (neutral)
	you are disparaged by your superior. (negative)
When you are with your romantic partner,	you and your partner are in love with each other. (positive)
	your partner asks you about tomorrow's weather (neutral)
	you break up with your partner. (negative)
When you think about marriage,	you can get married to your favorite person. (positive)
	you see a poster of a wedding hall. (neutral)
	you can't get married to anyone. (negative)
When you go on vacation,	you stroll through a park in the warm season. (positive)
	you try to remember the name of a tree. (neutral)
	you suffer from heat exhaustion. (negative)
When you propose to your romantic partner,	the proposal is accepted. (positive)
	a proposal has not been proffered yet. (neutral)
	the proposal is rejected. (negative)
When you look up,	the clearing blue sky has spread. (positive)
	you see an advertisement. (neutral)
	pigeon feces fall on your clothing. (negative)

2.2.6. Functional MRI data preprocessing and analysis

The initial eight volumes of each fMRI run were discarded owing to unsteady magnetization. Image and statistical analyses were performed using SPM8 software. Initially, EPI images were realigned to the first image, and then realigned to the mean image following the first realignment. We used slice-timing correction to adjust for differences in slice-acquisition times. We interpolated and re-sampled the data such that, for each time series, slices were acquired simultaneously with the reference slice, which was the middle slice. The high-resolution anatomical images were then co-registered to the mean of the functional images. The co-registered anatomical image was normalized to the Montreal Neurological Institute (MNI) atlas (Evans et al., 1994). The parameters from this normalization process were then applied to each of the functional images. Finally, the spatially normalized functional images were filtered using a Gaussian kernel with an FWHM of 8 mm in the x, y, and z axes. After preprocessing, the imagination phase-related activation was statistically evaluated on a voxel-by-voxel basis, using the general linear model at the individual level to generate contrast images. The introduction (2.5 s), imagination (15 s), and rating phases (5 s) were separately modeled by block design convolved with the canonical hemodynamic response. The introduction and rating phases were considered as covariates of no interest to partial out their contribution to brain activation in the single subject analyses. Using the three types of contrast images employed in the imagination phase (positive-LLC, neutral-LLC, negative-LLC; Fig. 1), we conducted a random-effects analysis at the group level (Friston, 2007) with a one-way within-subject ANOVA. We conducted a conjunction analysis using two subtraction images [(positive-LLC) − (negative-LLC)/(positive-LLC) − (neutral-LLC)]) to reveal the brain regions that were strongly activated in the positive condition. The statistical threshold was set at an uncorrected $p < 0.001$ at the voxel level and an FWE-corrected $p < 0.05$ at the cluster level (whole brain). The plot function in SPM8 was used to generate the plot of contrast estimates and 90% confidence intervals (CIs) at the voxels [−2, 36, −2] and [−8, 0, −2] in the three conditions; these contrast estimates were extracted from Matlab and used to create bar graphs. Furthermore, to assess the association between brain activity and self-evaluation score of the temporal happy feelings in the positive condition, we conducted a group analysis with a multiple regression design using the contrast image of the positive condition (positive-LLC) and VAS subtraction score (positive-LLC). Because we used the contrast images created by the 1st level analysis (positive-LLC, neutral-LLC, and negative-LLC) in the aforementioned 2nd level analysis, we used the contrast image of the positive condition and VAS subtraction score in this regression analysis. Based on the result of the conjunction analysis, an anatomical region of interest (ROI) in the rACC (Cingulum_Ant_L) was defined using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) from the Wake Forest University (WFU) Pickatlas (Maldjian et al., 2003) integrated in SPM8. To characterize the correlation in the ROI (rACC), the statistical threshold was set at an uncorrected $p < 0.001$ at the voxel level and at $p < 0.05$, FWE corrected, at the cluster level.

2.2.7. Voxel-based morphometry

A whole-brain, high-resolution T1-weighted anatomical MP-RAGE MRI was also acquired for each subject using the 3-Tesla MRI scanner (Verio; Siemens Ltd.). Similar to Experiment 1, anatomical brain images were processed using the VBM8 toolbox. After preprocessing of anatomical brain images, gray matter density in the rACC was examined for potential correlations with the response of the rACC in the positive condition. Based on the result of Experiment 1, an anatomical ROI in the rACC (Cingulum_Ant_L) was defined using the AAL atlas from the WFU Pickatlas. Using the contrast estimate at [−2, 36, −2] in the positive condition, which was determined by the aforementioned 2nd level analysis, as a covariate, we conducted a multiple regression analysis. To characterize correlations in the ROI (rACC), the statistical threshold was set at an uncorrected $p < 0.001$ at the voxel level and at $p < 0.05$, FWE corrected, at the cluster level.

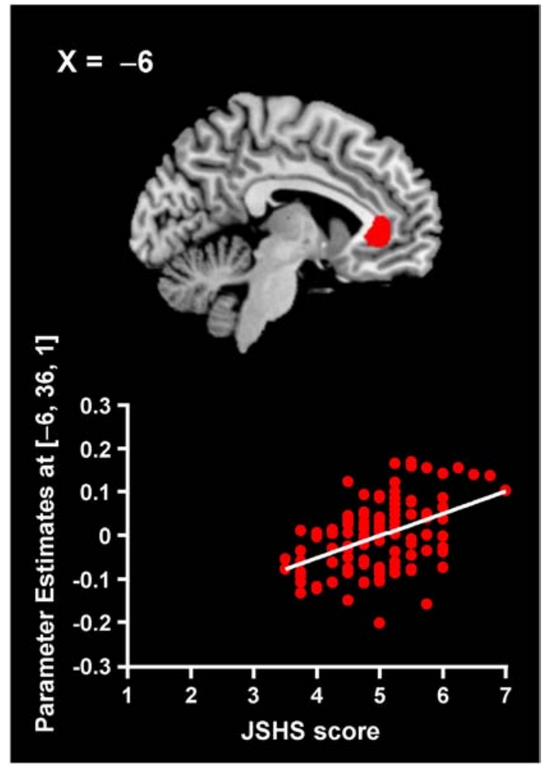

Fig. 2. Result of the VBM analysis. Statistical parametric map illustrating the cluster (red) positively associated with the JSHS score. The statistical threshold for the analysis was set at $p < 0.001$ (uncorrected) at the voxel level and $p < 0.05$ (FWE corrected; whole brain) at the cluster level. The scatter plot demonstrates the positive correlation between parameter estimates at [−6, 36, 1] (rACC) and JSHS scores. FWE: family-wise error; JSHS: Japanese version of Subjective Happiness scale; and rACC: rostral anterior cingulate cortex.

3. Results

3.1. Association between GMD of the rACC and subjective happiness (Experiment 1)

As depicted in Fig. 2, there was a significant positive correlation between JSHS scores and GMD of the rACC (peak coordinates: $x = -6, y = 36, z = 1$; $p < 0.05$, FWE corrected (whole brain); cluster size = 1019; $t = 5.28$). We did not observe significant positive correlations in other brain regions using this threshold or any significant negative correlations between GMD and JSHS scores.

3.2. Behavioral data (Experiment 2)

Fig. 3A shows the happiness ratings for the four conditions (positive, neutral, negative, and arithmetic). A repeated measures ANOVA revealed a significant main effect of condition on happiness rating scores ($F(3, 75) = 515.17$, $p < 0.01$). Multiple comparisons with Bonferroni correction indicated that happiness rating scores in the positive condition were significantly higher than those in the neutral ($p < 0.01$), negative ($p < 0.01$), and arithmetic LLC conditions ($p < 0.01$). Happiness rating scores in the neutral condition were significantly higher than those in the negative ($p < 0.01$) and LLC conditions ($p < 0.01$). Happiness ratings in the LLC condition were significantly higher than those in the negative condition ($p < 0.01$). Furthermore, JSHS scores were positively correlated with happiness rating scores in

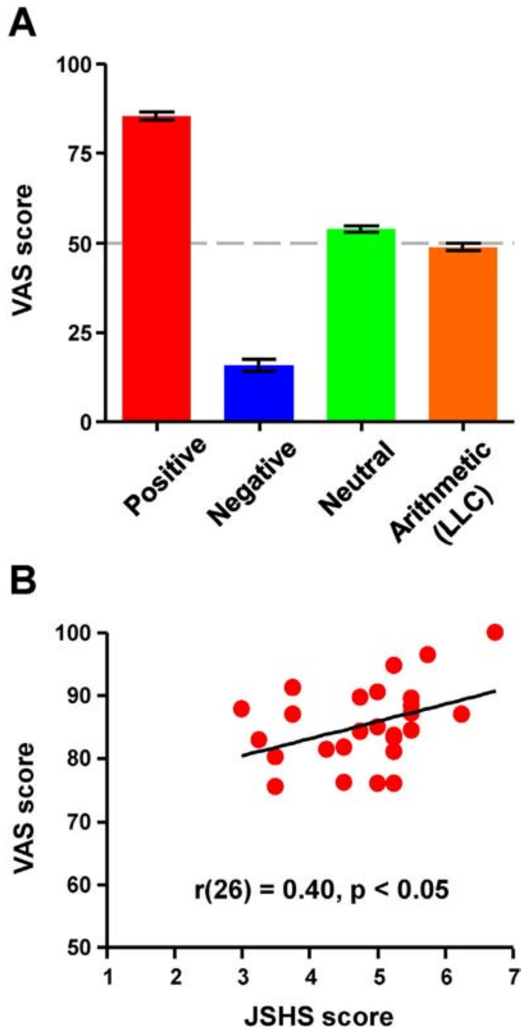

Fig. 3. Behavioral data in the functional MRI experiment. (A) Happiness rating scores in the positive, neutral, negative, and arithmetical conditions. Each column and error bar represents the mean ± SEM of the rating score, respectively ($n = 26$). (B) Scatter plot demonstrating the positive correlation between JSHS and happiness rating score in the positive condition. JSHS: Japanese version of Subjective Happiness Scale; LLC: low level control; and VAS: visual analog scale.

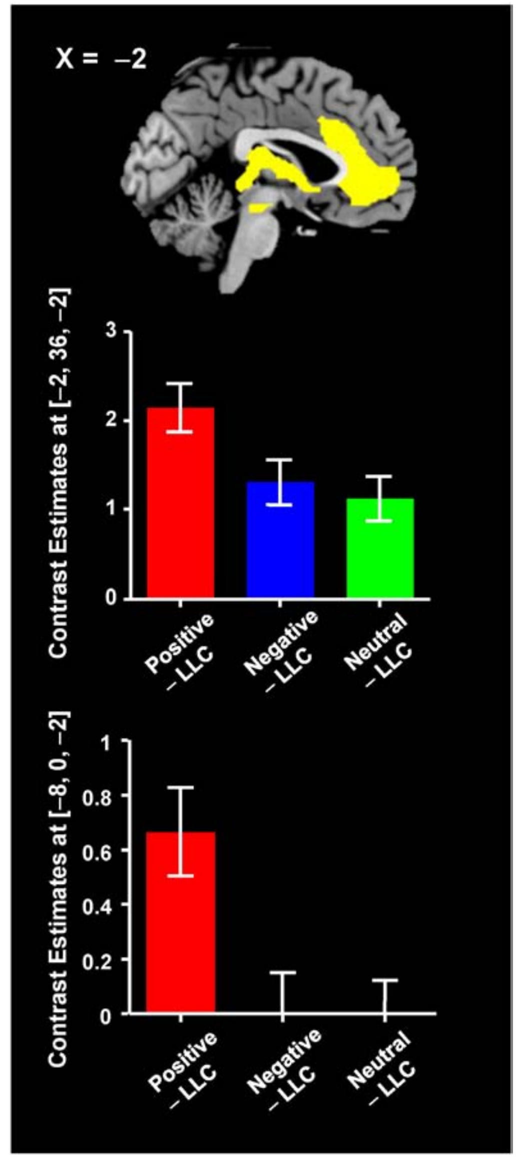

Fig. 4. Result of the subtraction and conjunction analyses in the functional MRI experiment. Statistical parametric map illustrating the cluster (yellow) that was significantly activated in the positive condition, as compared to the neutral and negative conditions. Statistical thresholds were set at $p < 0.001$ (uncorrected) at the voxel level and $p < 0.05$ (FWE corrected; whole brain) at the cluster level. Contrast estimates at [−2, 36, −2] (rACC) in each condition are denoted by the middle bar graph. Contrast estimates at [−8, 0, −2] (the lentiform nucleus) in each condition are denoted by the lower bar graph. Each column and error bar represents the mean ± SEM, respectively ($n = 26$). FWE: family-wise error; LLC: low level control; and rACC: rostral anterior cingulate cortex.

the positive condition ($r(26) = 0.41$, $p < 0.05$; Fig. 3B), whereas no correlations were observed for the neutral, negative, and LLC conditions.

3.3. Brain activations during positive emotion induction (Experiment 2)

We conducted subtraction and conjunction analyses to reveal the brain regions that were strongly activated in the positive condition. As shown in Fig. 4, the conjunction analysis using two subtractions [(positive-LLC) − (negative-LLC) / (positive-LLC) − (neutral-LLC)]) indicated that two large clusters were significantly activated in the positive condition. One cluster contained the prefrontal regions including the rACC (peak coordinates: x = −2, y = 36, z = −2; $p < 0.05$, FWE corrected (whole brain); cluster size = 2596; $t = 5.74$) (Fig. 4). The other cluster consisted of the brain regions including the thalamus and lentiform nucleus (peak coordinates: x = −8, y = 0, z = −2; $p < 0.05$, FWE corrected (whole brain); cluster size = 1871; $t = 5.20$). Subsequently, we assessed the association between self-ratings of happy feelings and brain activation. Because happy feelings were experienced only in the positive condition, we focused on the associations in this condition. The regression analysis using the contrast map of the positive condition (positive-LLC) and VAS subtraction score (positive-LLC) demonstrated that the self-evaluation score of the present happy feelings was positively correlated with the activity in the rACC (supragenual ACC) in the positive condition (peak coordinates: x = −6, y = 30, z = 14; $p < 0.05$, FWE corrected (ROI); cluster size = 20; $t = 4.52$; Fig. 5). We then assessed the association between the GMD of the rACC and the response of the rACC to positive stimuli. Using the contrast estimate at [−2, 36, −2] in the positive condition as a covariate, the VBM analysis was conducted to reveal the potential correlations with the rACC response in the positive condition. As shown in Fig. 6, the VBM analysis indicated a significant positive correlation between the GMD of the rACC and its response in the positive condition (peak coordinates: x = −6, y = 32, z = −3; $p < 0.05$, FWE corrected (ROI); cluster size = 139; $t = 4.32$).

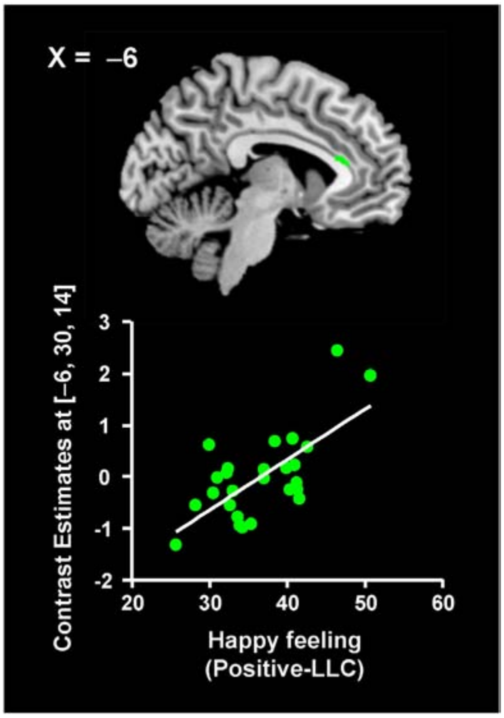

Fig. 5. Association between the rACC activity and temporal happy feelings. Statistical parametric map illustrating the cluster (green) that was significantly correlated with self-evaluation score of the temporal happy feelings (VAS subtraction score: positive-LLC) in the positive condition using the contrast image of the positive condition (subtraction image: positive-LLC). Statistical thresholds were set at $p < 0.001$ (uncorrected) at the voxel level and $p < 0.05$ (FWE corrected; ROI) at the cluster level. The scatter plot demonstrates the positive correlation between contrast estimates at [−6, 30, 14] (rACC) and VAS subtraction scores. FWE: family-wise error; LLC: low level control; rACC: rostral anterior cingulate cortex; and VAS: visual analog scale.

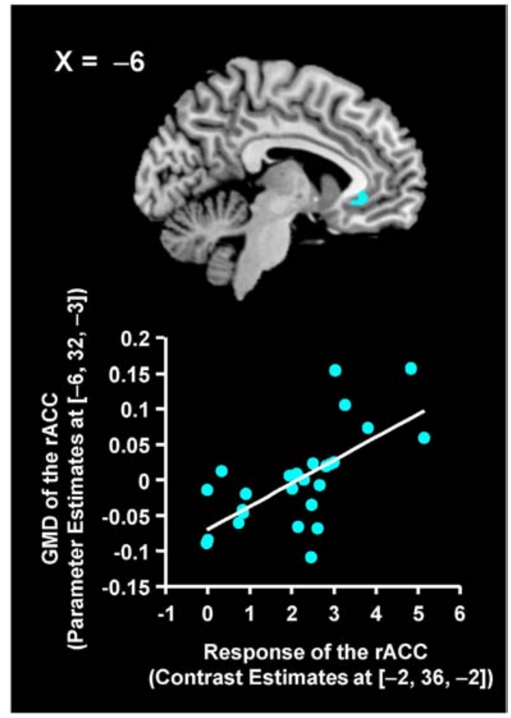

Fig. 6. Association between GMD of the rACC and response of the rACC to positive events in the fMRI experiment. Statistical parametric map illustrating the cluster (cyan) that was significantly correlated with the contrast estimate at [−2, 36, −2] (rACC) in the positive condition. The statistical threshold for the analysis was set at $p < 0.001$ (uncorrected) at the voxel level and $p < 0.05$ (FWE corrected; ROI) at the cluster level. The scatter plot demonstrates the positive correlation between parameter estimates at [−6, 32, −3] (GMD) and contrast estimates at [−2, 36, −2] (response). FWE: family-wise error; GMD: gray matter density; and rACC: rostral anterior cingulate cortex.

4. Discussion

4.1. Neural correlates of trait-like subjective happiness (Experiment 1)

In this study, we first investigated the association between GMD and JSHS scores via VBM. Experiment 1 demonstrated that individuals with high subjective happiness had greater rACC GMD (Fig. 2). The result of the rACC involvement in subjective happiness indicates that this region may be a trait-center for the feeling of happiness because no other region was identified in Experiment 1. The rACC was confirmed to be an affective division of the ACC and related to positive emotional states (Etkin et al., 2006, 2011). In fact, previous studies have shown that emotional laughter was associated with stronger activity in the rACC (Szameitat et al., 2010), and it was demonstrated that electrical stimulation of the rACC can induce laughter in humans (Caruana et al., 2015). Thus, the involvement of the rACC in subjective happiness seems to make sense.

However, previous structural MRI studies indicated that subjective happiness is related to other brain regions, such as the insular cortex (Lewis et al., 2014) and precuneus (Sato et al., 2015). One of the reasons for this discrepancy may be cultural differences in the concept of happiness. Previous studies indicated that the concept of happiness differs between countries (Oishi et al., 2013). In Japan, the concept of happiness is mainly linked to lucky or fortunate circumstances, whereas happiness is primarily linked to positive inner feelings in the United States, Spain, Argentina, Ecuador, and many other countries (Oishi et al., 2013). Thus, the neural correlates of happiness might differ between individuals from different countries. Indeed, a previous neuroimaging study in the United Kingdom demonstrated that experimentally induced happiness is associated with striatal activity (Rutledge et al., 2014), which is a region linked to positive inner states associated with reward (Berridge and Kringelbach, 2011). Another neuroimaging study from the United Kingdom also demonstrated an association between gray matter volume in the insular cortex and subjectively assessed eudemonic well-being (Lewis et al., 2014). These studies confirmed that the brain regions associated with inner states are also associated with happiness.

In contrast, a recent structural MRI study indicated an association between subjective happiness and gray matter volume in the precuneus in a Japanese sample (Sato et al., 2015). However, the present VBM did not reveal such an association between the precuneus and subjective happiness in our sample of Japanese participants. This may be due to large variation within the data set or the small sample size in the present study. In order to reveal the associations between other brain regions and subjective happiness, it will be necessary to conduct a neuroimaging study with a larger sample size.

4.2. Association between GMD of the rACC and its response to positive stimuli (Experiment 2)

In the second part of this study, we examined the associations between the BOLD response and the GMD of the rACC (Experiment 2, Fig. 1) by means of fMRI. Experiment 2 demonstrated that the life-event imagination task could induce temporal happy feelings in the positive condition (Fig. 3), and happiness rating scores in the positive condition were positively correlated with trait happiness level, whereas no correlations were observed for the neutral, negative, and LLC conditions (Fig. 3). This result replicated previous findings that individuals with a high trait-happiness level tended to evaluate their current emotional states more positively when they experienced positive events (Matsunaga et al., 2011b; Schimmack, 2008). The fMRI results indicated that the rACC was significantly activated in the positive condition, compared to the neutral and negative conditions (Fig. 4). Further, the VBM analysis showed that the GMD of the rACC was positively correlated with its response to positive events (Fig. 6). The results of Experiment 2 indicated that the high GMD of the rACC was involved in its increased response to positive stimuli, which may be linked to a more positive evaluation of the current emotional state. By combining the results of Experiments 1 and 2, we suggest that the biological mechanisms underlying the interaction between the two aspects of happiness might be explainable by the interaction between structure and function in the rACC.

However, we cannot conclude that a single region in the rACC is involved in subjective happiness because it appears that the activation area in the fMRI was located not only in the subgenual but also in the supragenual ACC, although the VBM area was located only in the subgenual ACC. These two areas, subgenual and supragenual ACC, are anatomically and functionally segregated in the human brain (Etkin et al., 2006, 2011). The supragenual ACC is involved in the evaluation of positive stimuli and computing the reward value (Etkin et al., 2006, 2011). In fact, the present fMRI result also indicated that the self-evaluation score of the present happy feelings was positively correlated with supragenual ACC activity (Fig. 5). In contrast, the subgenual ACC may have a role in autonomic regulation of emotional behavior, and dysfunction of the subgenual ACC is associated with mood disorders (Drevets et al., 2008; Du et al., 2012). Thus, the greater GMD of the subgenual ACC in happy people may be associated with maintaining a positive mood. Furthermore, the present fMRI experiment indicated that the brain regions including the thalamus and the lentiform nucleus were significantly activated in the positive condition (Fig. 4). The lentiform nucleus (putamen and globus pallidus) may be involved in hedonic brain circuits, and stimulation of this brain region elicits pleasure (Berridge and Kringelbach, 2011). The thalamus is known to regulate autonomic nervous activity, and previous studies have demonstrated that positive emotion induction can be linked to autonomic nervous activation (Kop et al., 2011). Thus, induction of a temporal state of happiness may be linked to activations in various brain regions.

4.3. Other interpretations about the association between the rACC and happiness

Although the rACC is anatomically separated from the medial prefrontal cortex (mPFC) by the cingulate sulcus, it is known that these prefrontal cortices are interconnected via the cingulate fasciculus (Etkin et al., 2011; Petrides and Pandya, 2007). Krueger et al. (2009) proposed the structural and temporal representation binding theory, which proposes that the mPFC represents event simulators (elators) that encompass a multi-modal representation of social event knowledge distributed throughout associated modality-specific areas. Elators, or abstract dynamic structured summary representations, provide the underlying properties of social cognitive structures involved in the planning and monitoring of one's own behavior and the comprehension and prediction of the behavior of others. Krueger et al. (2009) also proposed that the elator function is segregated along the dorsal–ventral axis. Specifically, goal knowledge, which supports inferences about the likely actions of agents aiming at goal achievement, is mediated by the dorsal mPFC pathway. In contrast, outcome knowledge, which supports inferences about the likely reward value accompanying the achievement of goals, is mediated by the orbital medial prefrontal/ventromedial prefrontal cortex pathway. The most rostral parts of the mPFC (rACC) allow for integration of information from both pathways. Thus, the rACC may act as an event simulator and involved in the reward estimation by integrating the information from dorsal and ventral pathways during the visualization of self-related events (Buckner and Carroll, 2007; Northoff and Bermpohl, 2004; Roy et al., 2012; Van Overwalle, 2009). In fact, previous neuroimaging studies have suggested that the rACC might play an important role in future reward estimation (Rushworth et al., 2011; Tanaka et al., 2004). It was demonstrated that participants' predictions of the value of future rewards are positively correlated with rACC activity (Tanaka et al., 2004).

The future reward estimation may be key factor in enhancing subjective happiness. The psychological self-concordance model of happiness advocated that self-concordant goal pursuit promotes sustained effort over time, which leads to greater progress towards goal achievement, more satisfying daily experiences, and finally positive changes in global happiness (Lyubomirsky et al., 2005; Sheldon and Houser-Marko, 2001). A self-concordant goal is able to initiate an “upward spiral” of positive outcomes: goal attainment leads to increased well-being and greater motivation to engage in any subsequent cycle of striving, which in turn leads to even greater attainment and further increases in well-being (Fredrickson, 2004; Lyubomirsky et al., 2005; Sheldon and Houser-Marko, 2001). If one expects positive outcomes, then one will work for the goals that have been set. However, if one expects failures, then one will disengage from the goals that have been set (Diener et al., 1999). Taken together, the enhanced function of the rACC may be linked to increased subjective happiness level.

In addition, previous studies have indicated that optimism, which is the tendency to expect good things, is related to happiness (Diener et al., 1999; Scheier and Carver, 1987; Taylor and Brown, 1988). Happy people tend to “look on the bright side” and rate events as pleasanter, have a more positive view of others, recall more positive events, and have pleasanter free associations (Argyle and Martin, 1991; Diener et al., 1999; Matsunaga et al., 2011b; Zhang et al., 2013). Interestingly, a previous neuroimaging study demonstrated that activity in the rACC during imagination of future positive events is positively correlated with trait optimism (Sharot et al., 2007), suggesting that the neural substrates underlying the relationship between optimistic illusion and happiness may also reside in the rACC.

4.4. Causal relationships between happiness and brain structure

The present study indicated that individuals with a large-volume trait-happiness-related brain region (rACC) had strong responses to positive stimuli and could easily experience happy feelings. These findings may be linked to the biological foundations of the psychological top-down theory of happiness, which postulates that personal traits influence temporal happy feelings. Previous studies have also showed that genetic traits, such as polymorphisms in the serotonin transporter gene-linked polymorphic region (5HTTLPR) and in the cannabinoid receptor 1 (CNR1) gene, are associated with the GMD of the rACC, rACC function, and subjective happiness level (Matsunaga et al., 2013, 2014; Pezawas et al., 2005). Thus, it is possible that the greater GMD of the rACC in individuals with a high subjective happiness level is congenitally determined. In contrast, the present findings also suggested that repetitive experience of happy events (repetitive stimulation of the rACC) could increase rACC volume, consistent with previous structural MRI studies (Driemeyer et al., 2008; Hamzei et al., 2012; Kwok et al., 2011). This may be a biological foundation of the psychological bottom-up theory of happiness, which postulates that repetitive positive events enhance trait happiness. However, the present study could not directly demonstrate such a relationship. More complex relationships might exist between happiness and brain structure; further studies are therefore required to corroborate these postulations.

4.5. Limitations

The present study has several limitations. First, the sample size might have been too small for VBM and fMRI studies, which could account for the dearth of findings beyond the rACC. Therefore, replication with a larger sample is important. Second, it is difficult to establish whether our results could be partly attributed to confounding factors, such as smoking, alcohol consumption, and other harmful activities, because we did not assess these factors. Third, although we assessed effects common to both sexes by using sex-matched samples in this study, sex differences may exist. For example, in the hypothetical situation used in the fMRI study, proposal to a romantic partner is more likely to be from a male to a female and less likely from a female to a male. Subjective happiness might differ between men and women. Thus, replication considering such gender-related differences would be important. Fourth, although the present fMRI task could induce temporal happy feelings, this task might be confusing with regard to past and future memories. For example, when "marriage" is used as a life event in the task, it was more likely a future than a past event for most of the present participants because they were relatively young. An event such as "party in the Japanese style pub," could be both a future and past event for the subjects. Thus, brain regions associated with the present task may be complex although a previous fMRI study demonstrated that imagining both past and future positive events can induce rACC activation (Sharot et al., 2007). Thus, in the future, we will have to conduct a neuroimaging study focused on the association between subjective happiness level and future and past event imagination.

Conclusion

The present findings indicate that the rACC is related to subjective happiness and suggest that the interaction between structure and function in the rACC can partly explain the interaction between trait-like subjective happiness and induction of event-related temporal happy feelings. This study reveals one of the neural foundations of subjective happiness. However, as mentioned above, we cannot conclude that a single region in the rACC is involved in subjective happiness. Thus, we will conduct further neuroimaging studies to reveal more precisely the neural bases of happiness.

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References

Argyle, M., Martin, M., 1991. The Psychological Causes of Happiness. In: Argyle, M., Schwarz, N. (Eds.), Strack, F. Subjective well-being. Pergamon Press, Oxford, pp. 77–100.
Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113.
Berridge, K.C., Kringelbach, M.L., 2011. Building a neuroscience of pleasure and well-being. Psychol. Well Being 1, 3. http://dx.doi.org/10.1186/2211-1522-1-3.
Buckner, R.L., Carroll, D.C., 2007. Self-projection and the brain. Trends Cogn. Sci. 11 (2), 49–57.
Caruana, F., Avanzini, P., Gozzo, F., Francione, S., Cardinale, F., Rizzolatti, G., 2015. Mirth and laughter elicited by electrical stimulation of the human anterior cingulate cortex. Cortex 71, 323–331.
Cerqueira, C.T., Almeida, J.R., Gorenstein, C., Gentil, V., Leite, C.C., Sato, J.R., Amaro Jr., E., Busatto, G.F., 2008. Engagement of multifocal neural circuits during recall of autobiographical happy events. Braz. J. Med. Biol. Res. 41 (12), 1076–1085.
Cook, S.C., Wellman, C.L., 2004. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J. Neurobiol. 60 (2), 236–248.
Craig, A.D., 2009. How do you feel—now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10 (1), 59–70.
Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat. Neurosci. 3 (10), 1049–1056.
Diener, E., 1984. Subjective well-being. Psychol. Bull. 95, 542–575.
Diener, E., 1994. Assessing subjective well-being: progress and opportunities. Soc. Indic. Res. 31, 103–157.
Diener, E., Suh, E.M., Lucas, R.E., Smith, H.L., 1999. Subjective well-being: three decades of progress. Psychol. Bull. 125, 276–302.
Drevets, W.C., Savitz, J., Trimble, M., 2008. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr. 13 (8), 663–681.
Driemeyer, J., Boyke, J., Gaser, C., Büchel, C., May, A., 2008. Changes in gray matter induced by learning-revisited. PLoS One 3 (7), e2669. http://dx.doi.org/10.1371/journal.pone.0002669.
Du, M.Y., Wu, Q.Z., Yue, Q., Li, J., Liao, Y., Kuang, W.H., Huang, X.Q., Chan, R.C.K., Mechelli, A., Gong, Q.Y., 2012. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 36 (1), 11–16.
Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51 (6), 871–882.
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15 (2), 85–93.
Evans, A.C., Kamber, M., Collins, D.L., MacDonald, D., 1994. An MRI-based Probabilistic Atlas of Neuroanatomy. In: Shorvon, S.D. (Ed.), Magnetic Resonance Scanning and Epilepsy. Plenum Press, New York, pp. 263–274.
Fredrickson, B.L., 2004. The broaden-and-build theory of positive emotions. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 359, 1367–1377.
Friston, K.J., 2007. Statistical Parametric Mapping. Academic Press, London.
Giménez, M., Junqué, C., Narberhaus, A., Caldú, X., Salgado-Pineda, P., Bargalló, N., Segarra, D., Botet, F., 2004. Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. NeuroImage 23 (3), 869–877.
Hamzei, F., Glauche, V., Schwarzwald, R., May, A., 2012. Dynamic gray matter changes within cortex and striatum after short motor skill training are associated with their increased functional interaction. NeuroImage 59 (4), 3364–3372.
Kanai, R., Rees, G., 2011. The structural basis of inter-individual differences in human behaviour and cognition. Nat. Rev. Neurosci. 12 (4), 231–242. http://dx.doi.org/10.1038/nrn3000.
Kanai, R., Bahrami, B., Duchaine, B., Janik, A., Banissy, M.J., Rees, G., 2012. Brain structure links loneliness to social perception. Curr. Biol. 22 (20), 1975–1979.
Kop, W.J., Synowski, S.J., Newell, M.E., Schmidt, L.A., Waldstein, S.R., Fox, N.A., 2011. Autonomic nervous system reactivity to positive and negative mood induction: the role of acute psychological responses and frontal electrocortical activity. Biol. Psychol. 86 (3), 230–238.
Krueger, F., Barbey, A.K., Grafman, J., 2009. The medial prefrontal cortex mediates social event knowledge. Trends Cogn. Sci. 13 (3), 103–109.
Kwok, V., Niu, Z., Kay, P., Zhou, K., Mo, L., Jin, Z., So, K.F., Tan, L.H., 2011. Learning new color names produces rapid increase in gray matter in the intact adult human cortex. Proc. Natl. Acad. Sci. U. S. A. 108 (16), 6686–6688.
Lewis, G.J., Kanai, R., Rees, G., Bates, T.C., 2014. Neural correlates of the 'good life': eudaimonic well-being is associated with insular cortex volume. Soc. Cogn. Affect. Neurosci. 9 (5), 615–618.
Lindquist, K.A., Wager, T.D., Kober, H., Bliss-Moreau, E., Barrett, L.F., 2012. The brain basis of emotion: a meta-analytic review. Behav. Brain Sci. 35 (3), 121–143.
Lyubomirsky, S., Lepper, H.S., 1999. A measure of subjective happiness: preliminary reliability and construct validation. Soc. Indic. Res. 46 (2), 137–155.
Lyubomirsky, S., Sheldon, K.M., Schkade, D., 2005. Pursuing happiness: the architecture of sustainable change. Rev. Gen. Psychol. 9 (2), 111–131.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19, 1233–1239.
Mårtensson, J., Eriksson, J., Bodammer, N.C., Lindgren, M., Johansson, M., Nyberg, L., Lövdén, M., 2012. Growth of language-related brain areas after foreign language learning. NeuroImage 63 (1), 240–244.
Matsunaga, M., Isowa, T., Yamakawa, K., Tsuboi, H., Kawanishi, Y., Kaneko, H., Kasugai, K., Yoneda, M., Ohira, H., 2011a. Association between perceived happiness levels and peripheral circulating pro-inflammatory cytokine levels in middle-aged adults in Japan. Neuro. Endocrinol. Lett. 32 (4), 458–463.
Matsunaga, M., Murakami, H., Yamakawa, K., Isowa, T., Fukuyama, S., Shinoda, J., Yamada, J., Ohira, H., 2011b. Perceived happiness level influences evocation of positive emotions. Nat. Sci. 3 (8), 723–727.
Matsunaga, M., Isowa, T., Yamakawa, K., Ohira, H., 2013. Association between the serotonin transporter polymorphism (5HTTLPR) and subjective happiness level in Japanese adults. Psychol. Well Being 3, 5. http://dx.doi.org/10.1186/2211-1522-3-5.
Matsunaga, M., Isowa, T., Yamakawa, Y., Fukuyama, S., Shinoda, J., Yamada, J., Ohira, H., 2014. Genetic variations in the human cannabinoid receptor gene are associated with happiness. PLoS One 9 (4), e93771. http://dx.doi.org/10.1371/journal.pone.0093771.
Mitterschiffthaler, M.T., Fu, C.H.Y., Dalton, J.A., Andrew, C.M., Williams, S.C.R., 2007. A functional MRI study of happy and sad affective states induced by classical music. Hum. Brain Mapp. 28 (11), 1150–1162.
Nakao, T., Ohira, H., Northoff, G., 2012. Distinction between externally vs. internally guided decision-making: operational differences, meta-analytical comparisons and their theoretical implications. Front. Neurosci. 6, 31. http://dx.doi.org/10.3389/fnins.2012.00031.
Northoff, G., Bermpohl, F., 2004. Cortical midline structures and the self. Trends Cogn. Sci. 8 (3), 102–107.

Oishi, S., Graham, J., Kesebir, S., Galinha, I.C., 2013. Concepts of happiness across time and cultures. Personal. Soc. Psychol. Bull. 39, 559–577.
Otake, K., Shimai, S., Tanaka-Matsumi, J., Otsui, K., Fredrickson, B.L., 2006. Happy people become happier through kindness: a counting kindness intervention. J. Happiness Stud. 7 (3), 361–375.
Oyama, Y., 2012. What makes people happy and what makes them unhappy? A cross-cultural qualitative study on the sense of happiness. Jpn. Psychol. Rev. 55, 90–106.
Petrides, M., Pandya, D.N., 2007. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J. Neurosci. 27 (43), 11573–11586.
Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R., 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat. Neurosci. 8 (6), 828–834.
Roy, M., Shohamy, D., Wager, T.D., 2012. Ventromedial prefrontal–subcortical systems and the generation of affective meaning. Trends Cogn. Sci. 16 (3), 147–156.
Rushworth, M.F., Noonan, M.P., Boorman, E.D., Walton, M.E., Behrens, T.E., 2011. Frontal cortex and reward-guided learning and decision-making. Neuron 70 (6), 1054–1069.
Rutledge, R.B., Skandali, N., Dayan, P., Dolan, R.J., 2014. A computational and neural model of momentary subjective well-being. Proc. Natl. Acad. Sci. U. S. A. 111 (33), 12252–12257.
Sato, W., Kochiyama, T., Yoshikawa, S., Naito, E., Matsumura, M., 2004. Enhanced neural activity in response to dynamic facial expressions of emotion: an fMRI study. Cogn. Brain Res. 20 (1), 81–91.
Sato, W., Kochiyama, T., Uono, S., Kubota, Y., Sawada, R., Yoshimura, S., Toichi, M., 2015. The structural neural substrate of subjective happiness. Sci. Report. 5, 16891. http://dx.doi.org/10.1038/srep16891.
Scheier, M.F., Carver, C.S., 1987. Dispositional optimism and physical well-being: the influence of generalized outcome expectancies on health. J. Pers. 55, 169–210.
Schimmack, U., 2008. The Structure of Subjective Wellbeing. In: Eid, M., Larsen, R.J. (Eds.), The Science of Subjective well-being. Guilford Press, New York, pp. 97–123.
Seligman, M.E.P., Steen, T., Park, N., Peterson, C., 2005. Positive psychology progress: empirical validation of interventions. Am. Psychol. 60 (5), 410–421.
Sharot, T., Riccardi, A.M., Raio, C.M., Phelps, E.A., 2007. Neural mechanisms mediating optimism bias. Nature 450 (7166), 102–105.
Sheldon, K.M., Houser-Marko, L., 2001. Self-concordance, goal attainment, and the pursuit of happiness: can there be an upward spiral? J. Pers. Soc. Psychol. 80 (1), 152–165.
Shimai, S., Otake, K., Utsuki, N., Ikemi, A., Lyubomirsky, S., 2004. Development of a Japanese version of the subjective happiness scale (SHS), and examination of its validity and reliability. Jpn. J. Public Health 51, 845–853.
Spampinato, M.V., Wood, J.N., De Simone, V., Grafman, J., 2009. Neural correlates of anxiety in healthy volunteers: a voxel-based morphometry study. J. Neuropsychiatr. Clin. Neurosci. 21 (2), 199–205.
Szameitat, D.P., Kreifelts, B., Alter, K., Szameitat, A.J., Sterr, A., Grodd, W., Wildgruber, D., 2010. It is not always tickling: distinct cerebral responses during perception of different laughter types. NeuroImage 53 (4), 1264–1271.
Tanaka, S.C., Doya, K., Okada, G., Ueda, K., Okamoto, Y., Yamawaki, S., 2004. Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. Nat. Neurosci. 7 (8), 887–893.
Taylor, S.E., Brown, J.D., 1988. Illusion and well-being: a social psychological perspective on mental health. Psychol. Bull. 103, 193–210.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.
Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum. Brain Mapp. 30 (3), 829–858.
Vytal, K., Hamann, S., 2010. Neuroimaging support for discrete neural correlates of basic emotions: a voxel-based meta-analysis. J. Cogn. Neurosci. 22 (12), 2864–2885.
Wellman, C.L., 2001. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. J. Neurobiol. 49 (3), 245–253.
Zhang, J.W., Howell, R.T., Stolarski, M., 2013. Comparing three methods to measure a balanced time perspective: the relationship between a balanced time perspective and subjective well-being. J. Happiness Stud. 14, 169–184.