ORIGINAL ARTICLE

Psychological and physiological responses to odor-evoked autobiographic memory

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Abstract

The "Proust phenomenon" occurs when a certain smell evokes a specific memory. Recent studies have demonstrated that odor-evoked autobiographic memories are more emotional than those elicited by other sensory stimuli because of the direct neural communication between the olfactory system and the amygdala. The amygdala is known to regulate various physiological activities including the endocrine and immune systems; therefore, odor-evoked autobiographic memory may trigger various psychological and physiological responses; however, the responses elicited by this memory remains obscure. In this study, we aimed to investigate the psychological and physiological responses accompanying odor-evoked autobiographic memory.

We recruited healthy male and female volunteers and investigated changes in their mood states and autonomic nervous, endocrine, and immune activities when autobiographic memory was evoked in the participants by asking them to smell an odor(s) that was nostalgic to them.

The autobiographic memories associated with positive emotion resulted in increased positive mood states, such as comfort and happiness, and decreased negative mood states, such as anxiety. Furthermore, heart rate was decreased, skin-conductance level was increased, and peripheral interleukin-2 level was decreased after smelling the nostalgic odor. These psychological and physiological responses were significantly correlated.

The present study suggests that odor-evoked autobiographic memory along with a positive feeling induce various physiological responses, including the autonomic nervous and immune activities. To the best of our knowledge, the present study is the first to observe an interaction between odor-evoked autobiographic memories and immune function.

Introduction

The phenomenon in which a certain smell evokes a specific memory – for example, the smell of a madeleine biscuit dipped in linden tea triggering intense joy and the memory of childhood (Proust, 1919) – is known as the "Proust phenomenon." Herz and colleagues recently characterized odor-evoked autobiographic memories to be more emotional than those elicited by other sensory stimuli through self-report and physiological responses (Herz & Cupchik, 1995; Herz, 1998; Herz & Schooler, 2002; Herz *et al* 2004). They demonstrated that the amygdala is strongly activated when autobiographic memories are evoked by olfactory cues compared to that by other sensory cues, such as a visual cue. The amygdala is known to be critical in the expression of emotion (Aggleton & Mishkin, 1986; LeDoux, 2000), and heightened activity of the amygdala represents intense emotional experience. The reason why the amygdala is strongly activated by odor may be the direct neural communication between the olfactory system and the amygdala. This is a feature that is unique to the olfactory sense (Aggleton & Mishkin, 1986; Cahill *et al* 1995).

Recent studies have demonstrated that the amygdala modulates various peripheral physiological responses such as the heart rate (HR), skin-conductance level (SCL), secretion of catecholamines, and secretion of cytokines, which are the immune-signaling molecules that modulate systemic inflammation, such as interleukin-2 (IL-2) and interleukin-6 (IL-6) (Ohira *et al* 2006; Maes *et al* 2011). Therefore, it is thought that an odor-evoked autobiographic memory may trigger various psychological and physiological responses, including the secretion of catecholamines and cytokines. Furthermore, previous studies in psychoneuroimmunology have demonstrated that evocation of positive emotions, such as happiness, influences our health and wellbeing through the modulation of our body's endocrine and immune functions (Matsunaga *et al* 2008; Matsunaga *et al* 2011a). It is known that odor-evoked autobiographic memory accompanies positive emotions (Herz & Cupchik, 1995; Herz, 1998; Herz & Schooler, 2002; Herz *et al* 2004). Thus, examining the effects of odor-evoked autobiographic memory along with positive emotions on psychological and physiological activities is warranted because odor-evoked autobiographic memory may have more remarkable effects on our health and wellbeing than other sensory-induced memories. In order to reveal any associations between odor-evoked autobiographic memories and activities of the autonomic nervous, endocrine, and immune systems, we assessed changes in mood states, heart rate, SCL, and plasma levels of catecholamines (norepinephrine and epinephrine) and cytokines (IL-2, interleukin-4 [IL-4], IL-6, interleukin-10 [IL-10], and tumor necrosis factor-α [TNF-α]) in the study participants when they experienced an odor-evoked autobiographic memory.

Material and Methods

Participants

Twenty-three healthy volunteers (5 men and 18 women) participated in this study. The age range of the participants was 21–38 years, and they all provided written informed consent in accordance with the Declaration of Helsinki. The participants received no medication during the experimental period. Women were examined during the late luteal and follicular first phases of their menstrual cycle when the secretion of female sex hormones is low, thus minimizing the influences of these hormones on the endocrine and immune systems. One participant was excluded from HR and blood sample analyses, and 4 other participants were excluded from the SCL analysis because of technical difficulties. This study was approved by the Ethics Committees of Nagoya University, Fujita Health University, and Kao Corporation.

Test stimuli

The participants themselves selected the odor that evoked an autobiographic memory for them before the day of the experiment. These odors were referred to as the nostalgic stimuli and included Christian Dior Hypnotic Poison, Yves Saint Laurent In Love Again, Chanel Allure, Gucci Envy, Angel Heart, Givenchy Insense Ultramarine, Emanuel Ungaro Apparition Sky, and L'Occitane Verbena. The control stimulus was a generic unmarketed perfume and was the same for all participants (obtained from Kao Corporation). Pretesting using 33 healthy volunteers established that the control odor did not evoke a sense of nostalgia nor an autobiographic memory.

Experimental procedure

Each participant entered an electrically shielded experimental chamber, following which electrodes were attached to his/her left arm and both legs to measure the autonomic nervous indices (HR and SCL). Next, a heparinized cannula was inserted into the participant's left forearm vein. The participant was given instructions prior to the commencement of the experiment. After a 10-min rest period in the chamber, the first blood sample was collected (for assaying baseline endocrine and immune parameters) and the participant was requested to evaluate his/her present mood state. Then, the participant was subjected to either the control odor (Control condition) or the nostalgic odor that would evoke an autobiographic memory (Proust condition) by asking the participant to smell the appropriate odor content (500 μL) in a micro tube held in the hand and brought to the nose for 30 s. After smelling its content for 30 s, to prevent adaptation to that particular smell, the participants were asked to take a rest from the smell for 30 s. After the 30 s rest period, they took a smell of it again for another 30 s. After the participant experienced the smell a second time, his/her blood sample

was collected and the mood state was assessed. This was followed by a 10-min rest period, after which the second odor-smelling session started. If they smelt the nostalgic stimulus first time, the second one would be the control stimulus and vice versa. All measurements were undertaken in a shielded room to minimize environmental noise that can be introduced by other external smells in the room. The order in which the 2 conditions were presented was counterbalanced across the participants.

Assessment of test stimuli

The perceived intensity of the test stimuli, pleasantness of the test stimuli, perceived arousal level, and evocations of sense of nostalgia and autobiographic memory were evaluated by rating it on the visual analog scale (VAS) as follows: intensity, complete scentless (0%)–extremely high intensity (100%); pleasantness, extremely negative (−100%)–neither (0%)–extremely positive (100%); arousal, extremely sleepy (−100%)–neither (0%)––extremely high arousal (100%); nostalgia, no nostalgia (0%)––extremely high nostalgia (100%); memory, no memory evocation (0%)––extremely high memory evocation (100%).

Measurement of mood states

To evaluate the mood states of the participants, they were asked to subjectively evaluate their present emotions by rating each of the following 9 questions on a scale of 1 (not at all) to 7 (yes, extremely): Do you feel peaceful at present? (comfort); do you feel uneasy at present? (anxiety); do you feel tired at present? (fatigue); do you feel highly energetic at present? (vigor); are you well at present? (comfort); are you relaxed at present? (relaxation); do you feel refreshed at present? (vigor); are you irritated at present? (irritation); do you feel happy at present? (happiness). The mood state rating scores were calculated with respect to each mood state of comfort, vigor, anxiety, fatigue, relaxation, irritation, and happiness. The mood states before and after smelling the test stimuli were assessed as described previously (Matsunaga *et al* 2009).

HR and SCL Measurement

HR and SCL were recorded using an MP-100 psychophysiological monitoring system (BioPac Systems, Santa Barbara, CA) as previously described (Ohira *et al* 2006). For the HR measurement, disposable Ag/AgCl electrodes were attached to the inner surface of the left arm and the outer surfaces of both lower legs of each participant. For the SCL measurement, Ag/AgCl electrodes filled with isotonic NaCl unibase electrolyte were attached to the volar surface of the second phalanx of the first and second fingers of the left hand of each participant. HR and SCL were continuously measured throughout the experiment, and the data were analyzed offline using the Acknowledge software (BioPac Systems). The cardiac interbeat interval was calculated as the interval between successive R waves. From these data, the mean HR and SCL during each period were calculated and statistically analyzed.

Measurements of catecholamine and cytokine concentrations

Blood samples taken to measure plasma catecholamine and cytokine levels were anticoagulated with ethylenediaminetetra-acetate, chilled, and centrifuged. The plasma was then removed and frozen at –80°C until analysis. Plasma epinephrine and norepinephrine levels were determined by high performance liquid chromatography. Alumina was used for extraction. The recovery rate for all amines was evaluated with a dihydroxybenzylamine standard and was between 60% and 70%. The intra-assay coefficient of variation was less than 5%, and the interassay variations were less than 6% for the measurement of epinephrine and norepinephrine (Mitsubishi Chemical Inc., Tokyo, Japan). Plasma cytokines (IL-2, IL-4, IL-6, IL-10, and TNF-α) were determined by a BD cytometric bead array (Human Th1/Th2 Cytokine Kit II; BD Biosciences, San Diego, CA) according to the manufacturer's instructions. The intra-assay coefficient of variation was less than 6%, and the interassay variations were less than 9% for the measurement of these cytokines.

Statistical analyses of self-reported mood states and the physiological data

Results are expressed as the mean ± standard error of mean (SEM). The control and nostalgic stimuli were compared by paired *t* tests. Physiological indices were compared using 2-way repeated measures ANOVA (condition [Control vs. Proust] × period [before vs. after]) followed by paired *t* tests. Furthermore, Pearson correlation coefficients were computed between the values of the psychological and physiological indices to examine the relationships between psychological and physiological activities.

Results

Evocation of autobiographic memory by odor

In order to assess whether the test stimuli evoked an autobiographic memory as well as a positive emotional valence, the participants were requested to evaluate the perceived intensity of test stimuli, pleasantness of test stimuli, perceived arousal level, and evocations of sense of nostalgia and autobiographic memory by using the VAS. Although there were no significant differences in the rating scores for perceived intensity, those for pleasantness (df=22, t=–5.12, p<0.01), arousal (df=22, t=–2.90, p<0.01), sense of nostalgia (df=22, t=–7.05, p<0.01), and autobiographic memory (df=22, t=–8.18, p<0.01) were significantly greater in the Proust condition than in the control condition (***Fig. 1***).

Effects of odor-evoked autobiographic memory on the mood states

The mood states were evaluated by a 7-scale rating system, which assessed the 7 different mood states, namely, comfort, vigor, anxiety, fatigue, relaxation, irritation, and happiness (***Tab. 1***). ANOVA indicated a significant main effect of the period (before and after) on the rating scores for vigor ($F(1,44)=11.56$, $p<0.01$), anxiety ($F(1,44)=4.68$, $p<0.05$), fatigue ($F(1,44)=16.06$, $p<0.01$), and happiness ($F(1,44)=5.42$, $p<0.05$). The paired t test revealed that the rating scores for comfort ($df=22$, $t=-2.48$, $p<0.05$) and happiness ($df=22$, $t=-2.12$, $p<0.05$) were significantly increased, whilst the rating score for anxiety was significantly decreased ($df=22$, $t=3.44$, $p<0.01$) after smelling the stimuli that induced the Proust condition. The rating score for vigor was significantly increased, whereas that for fatigue was significantly decreased, after smelling stimuli that evoked both the control and Proust conditions.

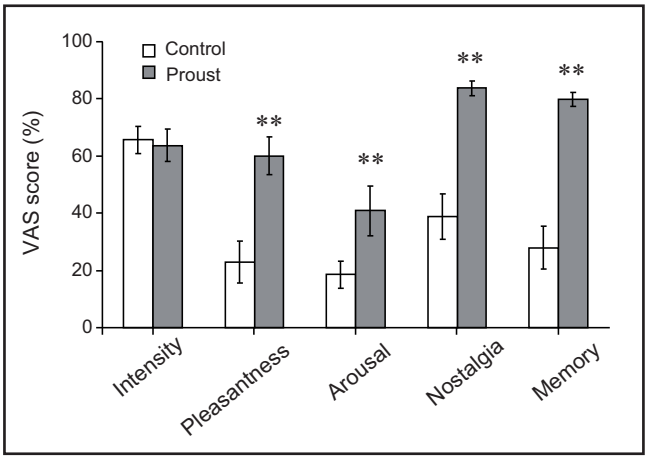

Fig. 1. Differences in the rating scores for characteristics of control and nostalgic odors. $^{**}p<0.01$ vs. control by paired t test

Effects of odor-evoked autobiographic memory on the autonomic nervous system indices

To examine whether odor-evoked autobiographic memory influenced HR and SCL, the participants' HR (***Fig. 2A***) and SCL (***Fig. 2B***) were measured during the experimental session. ANOVA revealed a significant main effect of the period (before and after) with regard to the difference in HR (***Fig. 2A***; $F(1,42)=7.52$, $p<0.01$) and SCL (***Fig. 2B***; $F(1,36)=15.66$, $p<0.01$). Further analysis using the paired t test indicated that HR decreased significantly (***Fig. 2A***; $df=21$, $t=2.63$, $p<0.05$), whilst SCL increased significantly, after smelling the test stimuli that evoked the nostalgic experience (***Fig. 2B***; $df=18$, $t=-4.30$, $p<0.01$).

Effects of odor-evoked autobiographic memory on plasma catecholamines and cytokines

To examine whether odor-evoked autobiographic memory influenced the peripheral levels of catecholamines and cytokines, we measured the plasma concentrations of norepinephrine, epinephrine, IL-2, IL-4, IL-6, IL-10, and TNF-α before and after the smelling sessions (***Tab. 2*** and ***Fig. 2C***). Although ANOVA indicated no significant differences in these indices, other statistical analyses using paired t tests indicated that the plasma level of IL-2 was significantly lower after smelling the test stimulus that evoked the Proust condition than that after the control condition (***Fig. 2C***; $df=21$, $t=2.49$, $p<0.05$).

Correlations among the psychological and physiological indices

Finally, to examine the associations among the psychological and physiological indices that were changed only in the Proust condition such as the pleasantness of the nostalgic odor; arousal; the sense of nostalgia; autobiographic memory; the mood states of comfort, anxiety, and happiness; HR; SCL; and the concentration of IL-2

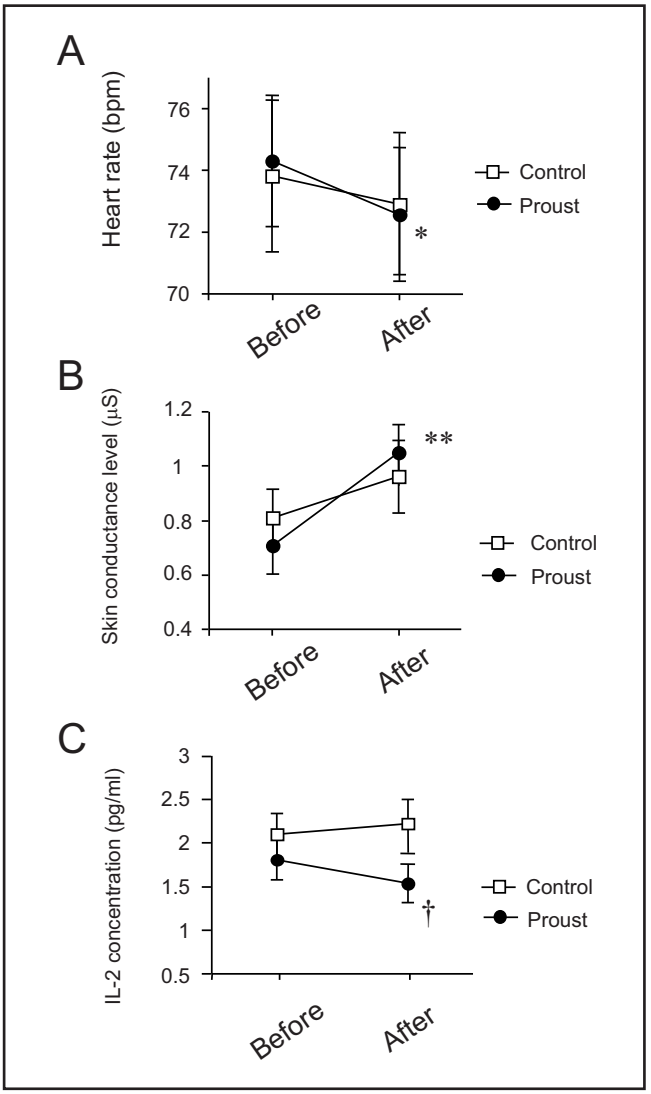

Fig. 2. (**A**) Change in heart rate (HR) after odor smelling. $^{*}p<0.05$ vs. before smelling by paired t test (**B**) Change in skin-conductance level after odor smelling. $^{**}p<0.01$ vs. before smelling by paired t test (**C**) Change in serum IL-2 levels after odor smelling. $^{\dagger}p<0.05$ vs. after control odor smelling by paired t test

Tab. 1. Self-rating of mood states such as pleasantness, vigor, anxiety, fatigue, relaxation, irritation, and happiness under control and Proust conditions.

Criterion	Control		Proust	
	Before	After	Before	After
Comfort	8.91±0.41	8.91±0.53	8.78±0.39	9.7±0.55*
Vigor	7.17±0.38	8.17±0.52**	7.21±0.50	8.34±0.53*
Anxiety	2.39±0.33	2.21±0.40	2.39±0.30	1.82±0.27**
Fatigue	3.30±0.37	2.82±0.36*	2.73±0.37	2.13±0.32**
Relaxation	4.60±0.27	4.73±0.31	4.60±0.33	4.91±0.22
Irritation	1.65±0.30	1.60±0.25	1.65±0.29	1.56±0.26
Happiness	3.69±0.28	3.86±0.36	3.82±0.43	4.39±0.39*

Each result represents the mean ± SEM rating score (n = 23 samples). *p<0.05, **p<0.01 versus before smelling, as determined by paired t tests

Tab. 2. Changes in the plasma levels of catecholamines and cytokines under control and Proust conditions.

Criterion	Control		Proust	
	Before	After	Before	After
Norepinephrine (ng/ml)	0.22±0.01	0.21±0.01	0.22±0.01	0.22±0.01
Epinephrine (ng/ml)	0.04±0.006	0.03±0.003	0.04±0.007	0.03±0.004
IL-4 (pg/ml)	4.14±0.63	4.95±0.84	3.92±0.60	4.30±0.69
IL-6 (pg/ml)	2.78±0.38	2.86±0.36	2.45±0.32	3.01±0.41
IL-10 (pg/ml)	2.86±0.41	3.02±0.37	2.74±0.43	2.82±0.35
TNF-α (pg/ml)	2.59±0.36	2.45±0.30	2.25±0.31	2.34±0.24

Each result represents the mean ± SEM levels (n = 22 samples)

in the plasma, the correlations among these indices were computed (***Tab 3***). The analyses indicated that the pleasantness of the nostalgic odor was positively correlated with arousal (r(46)=0.49, p<0.01), the sense of nostalgia (r(46)=0.62, p<0.01), autobiographic memory (r(46)=0.50, p<0.01), SCL change (r(38)=0.34, p<0.05), comfort score after smelling (r(46)=0.62, p<0.01), and happiness score after smelling (r(46)=0.52, p<0.01). It was negatively correlated with anxiety score after smelling (r(46)=−0.35, p<0.05) and IL-2 level after smelling (r(44)=−0.43, p<0.01). The arousal level was positively correlated with the sense of nostalgia (r(46)=0.41, p<0.01), SCL change (r(38)=0.40, p<0.05), and comfort score after smelling (r(46)=0.42, p<0.01). The sense of nostalgia was positively correlated with autobiographic memory (r(46)=0.87, p<0.01), SCL change (r(38)=0.36, p<0.05), comfort score after smelling (r(46)=0.37, p<0.01), and happiness score after smelling (r(46)=0.35, p<0.05), and negatively correlated with IL-2 level after smelling (r(44)=−0.43, p<0.01). The autobiographic memory was positively correlated with SCL change (r(38)=0.34, p<0.05), comfort score after smelling (r(46)=0.37, p<0.05), and happiness score after smelling (r(46)=0.35, p<0.05), and negatively correlated with IL-2 level after smelling (r(44)=−0.33, p<0.05). The rating score of comfort after smelling was positively correlated with happiness score after smelling (r(46)=0.62, p<0.01) and negatively correlated with anxiety score (r(46) =−0.50, p<0.01) and IL-2 level after smelling (r(44)=−0.34, p<0.05).

Discussion

In the present study, we first assessed whether our experimental method was appropriate. The participants were asked to evaluate the intensity and pleasantness of test stimuli, the levels of arousal, and the evocations of the sense of nostalgia and autobiographic memory. The levels of pleasantness, arousal, nostalgia,

Tab. 3. Pearson correlation coefficients among the psychological and physiological indices.

	Pleasantness	Arousal	Nostalgia	Memory	HR	SCL	Comfort	Anxiety	Happiness	IL-2
Pleasantness	–	0.49**	0.62**	0.50**	−0.19	0.34*	0.62**	−0.35*	0.52**	−0.43**
Arousal		–	0.41**	0.28	−0.05	0.40*	0.42**	−0.29	0.28	−0.27
Nostalgia			–	0.87**	−0.12	0.36*	0.37**	−0.10	0.35*	−0.43*
Memory				–	−0.16	0.34*	0.37*	−0.16	0.35*	−0.33*
HR					–	0.11	−0.03	0.01	−0.17	−0.08
SCL						–	0.27	−0.28	0.21	−0.25
Comfort							–	−0.50**	0.62**	−0.34*
Anxiety								–	−0.18	0.12
Happiness									–	−0.26

*p<0.05, **p<0.01

and autobiographic memory induced by the nostalgic odor were significantly higher than those induced by the control odor. This result indicated that the emotional valence and autobiographic memory evocation were different between control and nostalgic odors, although the intensities of both odors were similar. The nostalgic odor used in this study was specific to each individual and was an odor that evoked an autobiographic memory as well as a positive emotional valence . Thus, we are confident that our experimental method was appropriate. As the intensities of control and nostalgic odors were similar, any differences observed in the physiological responses between control and Proust conditions in the participants were likely to be due to the emotional arousal and the autobiographic memory evocation associated with the 2 conditions.

After the autobiographic memory evocation, the mood states of participants significantly changed. The positive feelings, such as comfort and happiness, were significantly increased, whilst the negative feelings, such as anxiety, were significantly decreased after smelling the nostalgic odor. The rating scores for these moods significantly correlated with autobiographic memory evocation and the sense of nostalgia; thus, it was indicated that the autobiographic memories were evoked along with the positive feelings. Furthermore, a significant decrease in HR and a significant increase in SCL were observed along with the autobiographic memory evocation. This phasic HR deceleration can be interpreted as an orienting response (Bradley *et al* 2001a,b), reflecting heightened attention and information intake. It is possible that the participants were intensely focused on smelling the nostalgic odor compared to the control odor. The SCL reflects mental sweating and is regulated by the sympathetic nervous system (Venables & Christie, 1980). The amygdala regulates autonomic nervous system activity, and a previous study has shown that activation of the amygdala is correlated with changes in SCL (Ohira *et al* 2006). The amygdala is known to be activated by both negative and positive emotional stimuli (Ohman, 2005; Paton *et al* 2006). In the present study, the rating score for positive emotions was positively correlated with changes in the SCL; therefore, the significant increase in the SCL shown in this study might reflect activation in the amygdala in response to the nostalgic odor.

Interestingly, the IL-2 levels decreased after smelling the nostalgic odor compared to those after the control odor. IL-2 is a molecule involved in immune system signaling and is normally produced by T lymphocytes during an immune response. Therefore, the decrease in peripheral IL-2 level may reflect inhibition of systemic inflammation. The odor-evoked autobiographic memory along with the positive feelings may have an inhibitory effect on systemic inflammation. Because our previous study demonstrated that the evocation of positive feelings such as happiness decreased peripheral circulating pro-inflammatory cytokine level (Matsunaga *et al* 2011a), the inhibitory effect of the odor-evoked autobiographic memory on systemic inflammation is conceivable. The mechanism as to how the odor-evoked autobiographic memory decreased peripheral IL-2 level is yet to be determined. One of the possible explanations is peripheral catecholamines. Peripheral catecholamine levels can change rapidly (Kimura *et al* 2007), and the cytokine release is shown to be related to catecholamine levels (Peng *et al* 2004). However, it is necessary to examine other influencing factors, as a change in catecholamine levels was not observed in the present study. A previous study indicated that the endocannabinoid system could inhibit IL-2 secretion from T cells (Kaplan *et al* 2005). This study showed that the IL-2 level after smelling was correlated with the evocations of positive emotion, and it is known that the endocannabinoid system is associated with positive emotion evocation (Chakrabarti *et al* 2006; Matsunaga *et al* 2011b). Thus, it is possible that stimulation of the endocannabinoid system by odor-evoked positive emotions suppressed IL-2 secretion. Furthermore, IL-2 secretion is known to be regulated by the cholinergic system (Nizri *et al* 2009). Activation of α7-nicotinic acetylcholine receptors attenuates inflammation via suppression of pro-inflammatory cytokine production, including that of IL-2 (Nizri *et al* 2009). It is well known that the cholinergic system is associated with memory (Blokland, 1996), and it is possible that the cholinergic system might have been stimulated when the nostalgic stimuli evoked the participants' autobiographic memory. Previous studies have indicated that IL-2 production is negatively correlated with the release of acetylcholine in the brain (Hanisch *et al* 1996). Based on these observations, it is also possible that stimulation of the cholinergic system by odor-evoked autobiographic memory suppressed IL-2 secretion in the present study.

Certain limitations of this study must be recognized. First, the relatively short experiment time (odor-smelling session = 1.5 min) was insufficient to determine the effects of the olfactory stimulation on endocrine and immune systems although previous studies have reported the significant short-time changes in endocrine and immune parameters (Ohira *et al* 2006; Kimura *et al* 2007). In the previous studies, changes in peripheral cytokine levels have been observed at least 30 min after the presentations of experimental stimuli; thus, change in peripheral IL-2 level shown in this study may be too fast. However, the previous studies have demonstrated that peripheral circulating lymphocytes that secrete several cytokines can be rapidly redistributed after emotional arousal (about 1–2 min; Kimura *et al* 2007). Thus, it is possible that the distribution of lymphocytes that secrete IL-2 in the blood may be changed after autobiographic memory evocation. The generalizability of the present findings must be further tested using a longer experiment time and lymphocyte distribution analyses. Second, some reports have noted gender differences with regard to the physiological

reactivity (Bosch *et al* 2005); however, we did not investigate the interaction effects with gender. In addition, interaction effects may exist with the order in which the two types of odors were presented. In a future study, we will attempt to investigate the interaction effects with order and gender.

The present study suggests that odor-evoked autobiographic memory could affect psychological and physiological activities, including immune activities, in the individual. It may also be the first study that shows an interaction between odor-evoked autobiographic memories and immune function. It is possible that the odor-evoked autobiographic memory might have beneficial effects on our health and wellbeing through inhibition of systemic inflammation. Future studies using neuroimaging techniques, such as positron emission tomography, will aid us in revealing associations between brain activities and psychological and physiological activities.

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Conflicts of Interest

No conflicts of interest exist.

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