Journal of the International Neuropsychological Society (2009), **15**, 990–1001.

doi:10.1017/S1355617709990403

Evaluative processing of ambivalent stimuli in patients with schizophrenia and depression: A [^{15}O] H_2O PET study

JAE-JIN KIM,[1,2,3] HAE-JEONG PARK,[1,2,3] YOUNG-CHUL JUNG,[1,2] JI WON CHUN,[1] HYE SUN KIM,[1]
JEONG HO SEOK,[4] NAM WOOK KIM,[2] IL HO PARK,[5] MAENG-GUN OH,[3] AND JONG DOO LEE[3]

[1]Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Gwangju Gyeonggi, Korea
[2]Department of Psychiatry, Yonsei University College of Medicine, Seoul, Korea
[3]Department of Radiology, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Psychiatry, Hallym University College of Medicine, Sacred Heart Hospital, Anyang, Korea
[5]Department of Psychiatry, Kwandong University College of Medicine, Myong-Ji Hospital, Koyang, Korea

(Received November 11, 2008; Final Revision June 12, 2009; Accepted June 15, 2009)

Abstract

Decision making in an emotionally conflicting situation is important in social life. We aimed to address the similarity and disparity of neural correlates involved in processing ambivalent stimuli in patients with schizophrenia and patients with depression. Behavioral task-related hemodynamic responses were measured using [^{15}O]H_2O positron emission tomography (PET) in 12 patients with schizophrenia and 12 patients with depression. The task was a modified word-stem completion task, which was designed to evoke ambivalence in forced and non-forced choice conditions. The prefrontal cortex and the cerebellum were found to show increased activity in the healthy control group. In the schizophrenia group, activity in these two regions was negligible. In the depression group, the pattern of activity was altered and a functional compensatory recruitment of the inferior parietal regions was suggested. The prefrontal cortex seems to be associated with the cognitive control to resolve the conflict toward the ambivalent stimuli, whereas the cerebellum reflects the sustained working memory to search for compromise alternatives. The deficit of cerebellar activation in the schizophrenia group might underlie the inability to search and consider compromising responses for conflict resolution. (*JINS*, 2009, *15*, 990–1001.)

Keywords: Conflict resolution, Ambivalence, Schizophrenia, Depression, PET, Prefrontal cortex, Cerebellum

INTRODUCTION

Decision making in a conflicting situation is one of the most important aspects in our social functioning. A state of simultaneous and opposite emotional tone and action tendency, so called ambivalence (Raulin & Brenner, 1993), often occurs in the social situation. Although ambivalence is now considered to be a normal phenomenon that underlies dilemmatic situations in everyday life, it was initially considered to be one of the fundamental symptoms of schizophrenia (Bleuler, 1950) and depression (Freud, 1917). Thereafter, different researchers have referred to different parts of the definition in addressing ambivalence in their patients, and the concept of ambivalence has been re-evaluated and extended beyond schizophrenia and depression (Billig et al., 1988; Sincoff, 1992). In consequence, epical research has remained limited and no study has yet elaborated the neural constructs of ambivalence in patients with schizophrenia and patients with depression.

Another problem inherent in measuring ambivalence is the issue that the simultaneous presence of positive and negative evaluations does not connote subjective ambivalence. Positive and negative evaluations can be held compromised and therefore ambivalence is more likely to be evoked when a dichotomous choice is required (Albertson, Brehm, & Alvarez, 2004). Previous studies (Keightley et al., 2003; Mitchell et al., 2007) indicated that brain activity during processing of emotional content is dependent on not only the type of stimuli but also the manner in which the stimuli are processed. We previously investigated whether the neural correlates involved in evaluative processing of ambivalent stimuli would

---

Correspondence and reprint requests to: Young-Chul Jung, Department of Psychiatry, Yonsei University College of Medicine, Severance Mental Health Hospital, 696-6 Tanbul-dong, Gwangju-si, Gyeonggi-do, Korea 464-100. E-mail: eugenejung@yuhs.ac

differ according to the response condition (forced choice *vs.* non-forced choice) in healthy participants (Jung et al., 2008). When forced to make a dichotomous evaluative judgment ("good" or "bad") of an ambivalent stimulus, the orbitofrontal cortex and ventrolateral prefrontal cortex were activated to resolve a conflict. In contrast, when a compromise alternative ("neither good nor bad") was available, only the orbitofrontal cortex was activated.

The purpose of this study was to examine the similarity and disparity of the neural correlates involved in conflict resolution during evaluative processing of ambivalent stimuli in patients with schizophrenia and patients with depression. To address this issue, we took advantage of the word-stem completion paradigm (Jung et al., 2008). The word-stem completion paradigm is primarily regarded as an example of perceptual priming. However, we modified the task by pairing two affectively valenced words with one monosyllabic word-stem. The affective valence of words was reported to influence cognitive processing when explicit memory was required in depressed patients (Danion et al., 1995), yet previous studies paired one univalent word (either with positive or negative valence) to one word-stem. We expanded this paradigm by pairing two univalent words with opposite valence to one word-stem and investigated the response pattern to resolve the emotional conflict when both positive and negative valence could be recollected simultaneously. It is well known that healthy participants show a negativity bias pattern, which refers to a tendency for the negative system to respond more than the positive system when emotional evaluative input increased (Ito, Larsen, Smith, & Cacioppo, 1998). We previously reported that patients with schizophrenia demonstrated blunted responses to negative emotional stimuli and lacked the ability to make compromise responses to neutral stimuli (Seok et al., 2006), whereas patients with depression are known to have enhanced attention to negative emotional stimuli (Norman, Miller, & Dow, 1988). Our hypothesis is that negative responses would be blunted in patients with schizophrenia, but strengthened in patients with depression, when forced to make a dichotomous response toward ambivalent stimuli. In addition, we hypothesized that both groups would lack the ability to make a compromise, even when compromise responses are available as an alternative. Given that the word-stem paradigm has been shown to recruit the prefrontal cortex and cerebellum (Buckner et al., 1995; Desmond, Gabrieli, & Glover, 1998) and that the prefrontal cortex was demonstrated to be involved in processing ambivalent stimuli (Cunningham, Johnson, Gatenby, Gore, & Banaji, 2003; Jung et al., 2006), these abnormal behavioral responses should be related with a distorted activity pattern of the prefrontal-cerebelluar circuit in the patient groups.

MATERIALS AND METHODS

Subjects

Participants included three age- and sex-matched groups consisting of 12 patients with schizophrenia, 12 patients with depression, and 12 healthy participants. Each group was composed of seven men and five women. All participants were right-handed. As shown in Table 1, the mean ages and mean periods of education were not significantly different among the groups. Patients with schizophrenia and patients with depression, who were recruited from the psychiatric outpatient clinic, fulfilled the DSM-IV-TR (American Psychiatric Association, 2000) criteria for their respective diagnoses. Exclusion criteria were any lifetime history of neurological or significant medical illnesses and any past history of substance abuse. Healthy participants were recruited from the community through Internet advertisements and screened to exclude cases with any current or lifetime history of a DSM-IV axis I disorder. At the time of recruitment, all patients had been clinically stable on a fixed-dose medication for at least 3 months. The scores of symptom severity were rated to be 48.3 (SD = 14.1) for the Positive and Negative Syndrome Scale (Kay, 1987) in the schizophrenia group and 34.0 (SD = 9.5) for the Beck Depression Inventory (Beck, Steer, & Brown, 1996) and 33.8 (SD = 11.1) for the Beck Anxiety Inventory (Beck & Steer, 1990) in the depression group. This study was carried out under the guidelines for the use of human participants established by the Institutional Review Board. Following a complete

Table 1. Demographic data of participants

	Healthy control	Schizophrenia	Depression	F/χ^2	*p*
Age (years)	24.8 (2.3)	24.6 (3.0)	23.9 (3.2)	0.330	0.721
Sex (M/F)	7/5	7/5	7/5	0.000	1.000
Education (years)	15.5 (1.9)	13.7 (1.7)	14.5 (1.7)	3.118	0.054
Duration of illness (years)	—	3.9 (2.3)	5.0 (4.2)	—	—
Beck Depression Inventory	7.7 (4.3)	13.3 (6.0)	34.1 (9.6)	47.626	<0.001
Beck Anxiety Inventory	8.4 (5.2)	20.8 (12.0)	33.8 (11.1)	19.547	<0.001
Positive and Negative Syndrome Scale					
Positive		11.1 (3.1)			
Negative		12.6 (4.4)			
General		24.7 (7.2)	—	—	—

description of the scope of the study to all participants, written informed consent was obtained.

Task Description

The task has been described in detail elsewhere (Jung et al., 2008). We developed a word-stem competition task using one of the characteristics of the Korean language; the majority of nouns are disyllabic words, and it is common for disyllabic words to share an identical monosyllabic word-stem. We used 16 monosyllabic word-stems that had no semantic meanings by themselves in conjunction with 16 disyllabic word pairs. The pairs of disyllabic words were categorized into three groups: positive-positive (e.g., "***chin***-*jul* [kindness]" and "***chin***-*gu* [friend]"), negative-negative (e.g., "***go***-*nan* [suffering]" and "***go***-*mun* [torture]"), and positive-negative (e.g., "***sa***-*lang* [love]" and "***sa***-*mang* [death]"). Consequently, monosyllabic word-stem cues were categorized into either a univalent positive (e.g., [***chin***]), univalent negative (e.g., [***go***]) or ambivalent stimulus (e.g., [***sa***]) group.

The task consisted of two phases (Figure 1). In the study phase, participants responded by pressing one of two buttons to indicate "good" or "bad." Each word was presented with an emotionally congruent background picture that was created by modifying photographs from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1998) to strengthen the subjective feeling. The number of good and bad stimuli was equivalent and each stimulus was presented for 2700 ms at 300-ms intervals. The stimuli were presented randomly and repeated four times. In the test

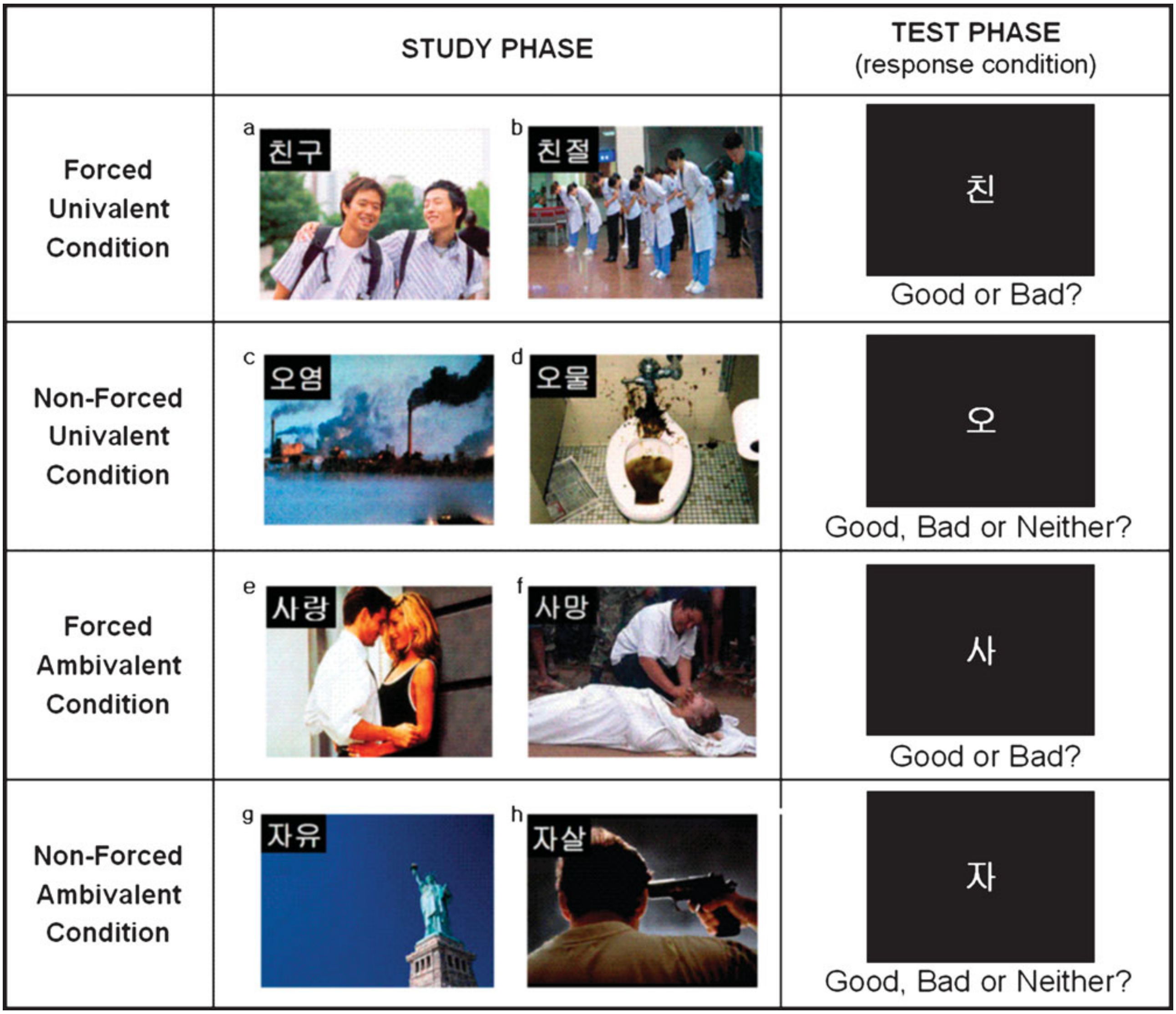

Fig. 1. Modified word-stem completion paradigm. Two words of opposite emotional valence from the study phase were designed to be recalled by one word-stem during the test phase. During the non-forced ambivalent condition, participants could respond with "good," "bad," or "neither-good-nor-bad." However, during the forced ambivalent condition, participants had to make a dichotomous choice between either "good" or "bad." [a][chin-gu] (friend), [b][chin-jeol] (kindness); [c][oh-yeom] (pollution), [d][oh-mul] (sewage); [e][sa-lang] (love), [f][sa-mang] (death); [g][ja-yoo] (freedom), [h][ja-sal] (suicide).

phase, a monosyllabic word-stem was presented on a black background, and participants were instructed to "respond according to the subjective feeling elicited when trying to complete each word-stem with a word from the preceding study phase." The test phase included four different blocks: (1) a non-forced univalent condition (nFU); (2) a forced univalent condition (FU); (3) a non-forced ambivalent condition (nFA); and (4) a forced ambivalent condition (FA). Each block was composed of eight monosyllabic word-stem cues. The first two univalent conditions were composed of four positive and four negative univalent word-stems, whereas the last two ambivalent conditions were composed of four ambivalent word-stems together with two positive and two negative word-stems. During the non-forced ambivalent condition, participants could respond with "good," "bad," or "neither-good-nor-bad" to make use of the compromise response. However, during the forced ambivalent condition, participants had to make a dichotomous choice between either "good" or "bad," and thus had to confront an ambivalent situation because two words of contradictory valence were recalled by the ambivalent word-stem cue. Each monosyllabic word-stem cue was presented for 2700 ms at 300-ms intervals and repeated six times. The sequence of the blocks was randomized.

Before performing the task, the valence of each stimulus (disyllabic words and monosyllabic word-stems) was determined by asking participants to rate on a 5-point Likert scale: 1 (strong negative), 2 (weak negative), 3 (neutral), 4 (weak positive), and 5 (strong positive). Positive words were rated to be 4.6 (SD = 0.4) in the schizophrenia group, 3.8 (SD = 0.9) in the depression group, and 4.3 (SD = 0.4) in the healthy controls, whereas negative words were rated to be 1.4 (SD = 0.5), 1.7 (SD = 0.5), and 1.5 (SD = 0.2), respectively. A significant difference in the mean valence among the groups was observed in positive words ($F = 5.363$; $df = 2$; $p = .010$), but not in negative words. Meanwhile, monosyllabic word-stems were rated to be 3.3 (SD = 0.4), 2.9 (SD = 0.3), and 3.3 (SD = 0.4), respectively. There was a significant difference in the mean valence of the word-stem ($F = 6.669$; $df = 2$; $p = .004$) among the groups (Appendix).

Image Data Acquisition and Data Processing

Scans were obtained using a Philips GEMINI PET/CT scanner (Cleveland, OH). In each block, an intravenous bolus injection of approximately 370 MBq of $[^{15}O]H_2O$ was given in the antecubital vein of the left forearm through an intravenous line. PET data were acquired over a 120-s time period. Four scans at 15-min intervals were acquired per participant during the test phase, and practicing the study phase took place during the interval before each scanning. The correction for tissue attenuation was based on the data of low-dose CT transmission measurements. The acquired images were reconstructed using the three-dimensional row-action maximum likelihood algorithm (3D-RAMLA). List-mode data were binned into sinograms, allowing frame durations to be determined after acquisition. Images were reconstructed based on a time-activity curve using a 20- to 120-s interval. Spatial preprocessing and statistical analysis were performed using Statistical Parametric Mapping 2 (Department of Neurology, University College of London, London, UK). All reconstructed images were realigned and transformed into a standard Talairach space (Talairach & Tournoux, 1988) using affine and non-linear transformation to remove participant anatomical variability. Spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel of 10-mm full width at half maximum (FWHM).

Statistical Analysis

At first, contrasts were generated to test for voxel-wise effects of differences between blocks within each group. The first contrast, referred to as "non-forced ambivalence," was made by the comparison between the non-forced ambivalent condition and the univalent conditions [2nFA – (nFU + FU)]. The second contrast, referred to as "forced ambivalence," was made by the comparison between the forced ambivalent condition and the univalent conditions [2FA – (nFU + FU)]. Because behavioral responses in the univalent conditions were quite similar regardless of the choice conditions, images of the univalent conditions were used collectively to increase the signal-to-noise ratio. Compared with the univalent conditions, relative increases in each of the non-forced and forced ambivalent conditions were separately counted. The threshold of significance was defined as exceeding an uncorrected p level of .001. After within-group comparison, we performed analysis of variance to make direct statistical comparison of brain responses between the three groups for both the "non-forced ambivalence" contrast and the "forced ambivalence" contrast. The threshold of significance was defined as exceeding an uncorrected p level of .001.

Post hoc analysis was performed to evaluate the correlations between regional activity. The adjusted mean regional activity (Kim et al., 2005) was calculated by averaging values of the condition-specific adjusted rCBF for all voxels within the regions of interest (ROIs) corresponding to the clusters of significant contiguous voxels identified by the within-group comparisons. Percent changes in regional activity were calculated with the following formula: 100 × (AMBI-UNI)/UNI, in which AMBI was the adjusted mean regional activity during ambivalent conditions and UNI was the adjusted mean regional activity during univalent conditions. Pearson correlations between the percent changes between the ROIs were computed in each group. The significance of the correlation was accepted when $p < .05$.

RESULTS

Behavioral Responses

To interpret behavioral measures, we defined the most common response of the healthy controls as the accurate one and performed analysis of variance using the diagnosis as a between-group factor. The behavioral responses are summarized in Table 2.

During the non-forced ambivalent condition, responses to ambivalent stimuli were significantly different among groups ($F=5.645$; $df=2.33$; $p=.008$; Figure 2A). The healthy control group and depression group preferred to make compromise responses. In contrast, the schizophrenia group tended to assign a positive valence to ambivalent stimuli and did not make use of the compromise option, which is consistent with our hypothesis. During the forced ambivalent condition, contrary to our expectations, neither blunting of negative responses nor accentuation of positive responses was observed in the patient groups. There was no difference in responses to ambivalent stimuli among the groups ($F=1.582$; $df=2.33$; $p=.222$; Figure 2B).

Within-Group Analysis

Non-forced ambivalence

The healthy control group demonstrated increased activity in the left orbitofrontal cortex (BA 11) and the cerebellum. The schizophrenia group demonstrated increased activity in the supplementary motor area (BA 6) and the lingual gyrus (BA 18). The depression group demonstrated increased activity in the left orbitofrontal cortex (BA 11), left inferior parietal lobule (BA 40), and several areas within the cerebellum (Table 3; Figure 3A).

Forced ambivalence

The healthy control group demonstrated increased activity in the right frontopolar area (BA10), the left orbitofrontal cortex (BA11), the right ventrolateral prefrontal cortex (BA 44), the thalamus, and the cerebellum. The schizophrenia group demonstrated increased activity in the ventrolateral prefrontal cortex (BA 45), the supplementary motor area (BA 6), and the anterior cingulate cortex (BA 32). The depression group demonstrated increased activity in the supplementary motor area (BA 6), the thalamus, and the cerebellum (Table 3; Figure 3B).

Between-Group Analysis

Non-forced ambivalence

There were significant differences of activity in the prefrontal cortex and the cerebellum between the groups (Table 4). Activity of the right cerebellum was significantly increased

Table 2. Mean % of responses, according to the stimulus and response conditions

	Non-forced choice condition			Forced choice condition		
Type of stimuli and responses	Healthy	Schizophrenia	Depression	Healthy	Schizophrenia	Depression
Univalent condition						
Positive stimulus						
Missing	0.3±1.1	2.6±7.8	1.9±3.3	0.6±1.4	2.2±7.8	0.8±2.4
Good	98.7±3.4	93.6±12.0	95.4±7.0	99.4±1.5	94.6±9.5	97.3±7.3
Bad	1.0±3.3	1.9±3.8	2.3±3.7	0.0±0.0	3.2±5.1	1.9±4.9
Neither good nor bad	0.0±0.0	1.9±4.8	0.4±1.2	—	—	—
Negative stimulus						
Missing	0.7±1.6	2.1±7.2	0.4±1.3	0±0.0	1.7±6.0	0.4±1.3
Good	1.4±2.1	2.8±4.1	5.8±7.1	0.3±1.2	3.5±4.6	3.8±4.6
Bad	97.9±2.8	92.4±12.0	93.3±9.3	99.7±1.2	94.8±6.7	95.8±5.2
Neither good nor bad	0.0±0.0	2.8±7.4	0.4±1.3	—	—	—
Ambivalent condition						
Positive stimulus						
Missing	1.3±4.4	4.5±13.3	3.1±9.7	0.7±2.4	0.0±0.0	2.8±8.3
Good	93.6±10.8	91.7±17.5	94.6±9.6	99.3±2.4	95.1±9.7	95.4±11.1
Bad	1.3±4.4	3.2±5.1	1.5±3.2	0.0±0.0	4.9±9.7	1.9±3.7
Neither good nor bad	3.8±7.7	0.6±2.2	0.8±2.4	—	—	—
Negative stimulus						
Missing	1.3±3.0	4.5±11.1	3.8±7.5	0.0±0.0	1.3±4.4	2.6±7.7
Good	6.4±11.3	1.9±4.8	0.0±0.0	3.8±6.1	3.2±5.1	5.1±8.6
Bad	90.4±18.0	89.7±11.5	93.8±11.9	96.2±6.1	95.5±7.7	92.3±15.4
Neither good nor bad	1.9±6.7	4.5±6.1	2.3±5.2	—	—	—
Ambivalent stimulus						
Missing	1.0±1.9	7.3±17.6	2.9±7.9	3.3±9.2	3.3±7.0	1.8±2.9
Good	15.3±23.7	43.4±26.9	15.0±23.7	61.3±16.0	61.0±17.3	50.2±12.8
Bad	6.3±12.8	22.2±21.1	16.3±28.2	35.3±16.7	35.7±16.7	48.0±14.3
Neither good nor bad	77.4±36.8	27.1±32.2	65.8±46.0	—	—	—

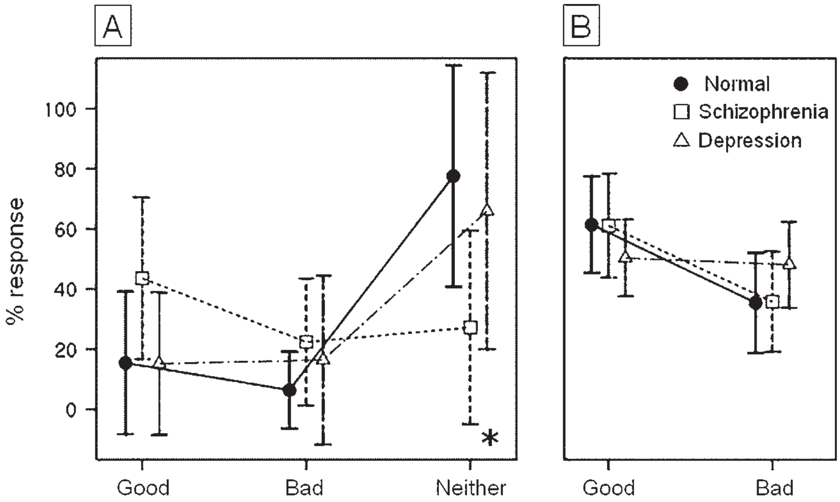

Fig. 2. Behavioral responses to ambivalent stimuli. During non-forced ambivalent conditions (A), the percentage of "neither-good-nor-bad" responses was significantly lower in patients with schizophrenia than in the other two groups (*$p < .05$). During forced ambivalent conditions (B), there was no significant difference between groups.

in the healthy control group compared with the schizophrenia group. Activity of the left frontopolar area (BA 10) was significantly increased in the healthy group compared with the depression group.

Forced ambivalence

There were significant differences of activity in the prefrontal cortex and the cerebellum between the groups (Table 4). Activity of the right orbitofrontal cortex (BA 11) and the right frontopolar area (BA10) was increased in the healthy control group compared with the schizophrenia group. Activity of the right frontopolar area (BA10) and the cerebellar vermis were increased in the healthy control group compared with the depression group.

Correlations Between Regional Activity Changes of the Cerebellum and Orbitofrontal Cortex

The mean adjusted percent changes of ROI regional activity are shown in Table 3. During non-forced ambivalence, activity changes in the ROI within the right cerebellum (x: 30, y: −56, z: −24) demonstrated a dichotomous activation pattern (Figure 4A). In healthy participants, the right cerebellum was only activated in participants who made compromise responses ($n = 10$) and was not activated in participants who did not make compromise responses ($n = 2$). Among the participants who made compromise responses, activity changes of the right cerebellum showed significant correlation with those of the left orbitofrontal cortex (x: −20, y: 48, z: −26; $r = 0.683$; $p = .030$; Figure 4B). In the schizophrenia group, significant correlations were not observed. In the depression group, there was a correlation trait between activity changes in the ROI within the cerebellum (x: 4, y: −62, z: −10) and those within the inferior parietal lobule (x: −56, y: −30, z: 52; $r = 0.514$; $p = .105$).

DISCUSSION

This is the first study to compare behavioral response and neural correlates involved in evaluative processing of ambivalent stimuli in patients with schizophrenia and patients with depression. During the non-forced ambivalent condition, the behavioral responses differed between groups, which might be linked with the distorted activation pattern of the prefrontal cortex and the cerebellum demonstrated in the disease groups. During the forced ambivalent condition, distorted activation patterns of the prefrontal cortex and the cerebellum were evident, but there was no significant difference of behavioral response between groups.

Behavioral Responses

During the non-forced ambivalent condition, patients with schizophrenia preferred to make dichotomous responses between "good" or "bad," which reflects the deficit of considering a compromise response in ambivalent situations. Dichotomous responses refer to a tendency to evaluate experiences in terms of mutually exclusive categories rather than to regard experiences as falling along a continuum (Linehan, 1993). These findings are consistent with the viewpoint of Bleuler (1950), who proposed that patients with schizophrenia have difficulty forming an integrated conceptualization of both good and bad in a given object.

Although there was no significant difference among groups in the forced-ambivalent condition, it is noteworthy that the healthy participants and the schizophrenia patients followed a pattern of the positivity offset (Cacioppo et al., 1999; Peeters & Czapinski, 1990). This should be linked to the fact that we induced emotion by retrieving emotional words and pictures rather than presenting them directly, therefore the emotional input should have been weak.

Table 3. Within-group comparison of increased activations during ambivalent conditions

		Non-forced Ambivalent > Univalent						Forced Ambivalence > Univalent					
	Region[a]	Voxels	Zmax	Coordinates (x, y, z)			Mean (SD) percent change[b]	Voxels	Zmax	Coordinates (x, y, z)			Mean (SD) percent change[b]
Healthy	R. superior frontal (BA 10)							432	3.78	32	64	2	4.1 (3.6)
	L. orbitofrontal (BA 11)	18	3.31	−20	48	−26	4.5 (4.2)	13	3.19	−32	56	−4	3.6 (3.9)
	R. inferior frontal (BA 44)							89	3.70	48	16	12	3.5 (1.9)
	R. middle frontal (BA 6)							66	3.59	50	22	44	4.4 (3.8)
	L. thalamus							7	3.20	−14	−12	8	3.5 (3.7)
	Cerebellar vermis	17	3.35	2	−72	−40	3.3 (3.5)	200	4.26	2	−72	−40	4.2 (4.3)
	R. cerebellum	23	3.63	10	−86	−50	5.6 (5.4)						
		38	3.46	30	−56	−24	3.4 (3.1)						
	L. cerebellum	39	3.82	−52	−58	−48	4.7 (2.8)						
Schizophrenia	R. inferior frontal (BA 45)							74	3.58	44	14	20	3.8 (3.9)
	R. middle frontal (BA6)							29	3.54	40	22	56	4.3 (3.4)
	L. middle frontal (BA 6)	51	3.62	−32	18	58	5.0 (4.2)						
	R. superior frontal (BA 6)							9	3.19	14	20	50	4.8 (6.1)
	L. anterior cingulate (BA 32)							7	3.30	−14	16	32	4.1 (5.8)
	L. lingual (BA 18)	16	3.32	−8	−88	−20	3.4 (3.0)						
Depression	L. orbitofrontal (BA 11)	11	3.39	−12	40	−36	6.8 (7.5)						
	R. superior frontal (BA 6)							11	3.51	10	36	60	4.9 (5.7)
	L. supramarginal (BA 40)	48	3.40	−56	−30	52	4.8 (5.6)						
	R. thalamus							16	3.30	26	−18	12	3.9 (4.2)
	cerebellar vermis	857	4.34	4	−62	−10	4.2 (3.7)	44	3.49	0	−48	−38	3.9 (2.7)
		152	4.03	−8	−48	−42	4.2 (3.8)	5	3.16	8	−56	−48	3.7 (2.8)
	R. cerebellum	116	3.86	30	−40	−36	4.2 (2.8)						
		9	3.21	36	−64	−32	3.1 (3.0)						
	L. cerebellum	480	4.01	−30	−62	−40	3.7 (3.6)	469	4.28	−30	−68	−44	3.8 (2.1)
								55	3.67	−20	−92	−32	3.6 (2.5)

Note. We edited the results of decreased activations in this table.

[a] The threshold of significance for the clusters was defined as exceeding an uncorrected p level of .001 and containing at least five contiguous voxels.

[b] Percent change was calculated by [100 × (AMBI – UNI)/UNI]: AMBI indicates the mean regional activity during the ambivalent condition block, and UNI indicates the mean regional activity during the univalent condition blocks.

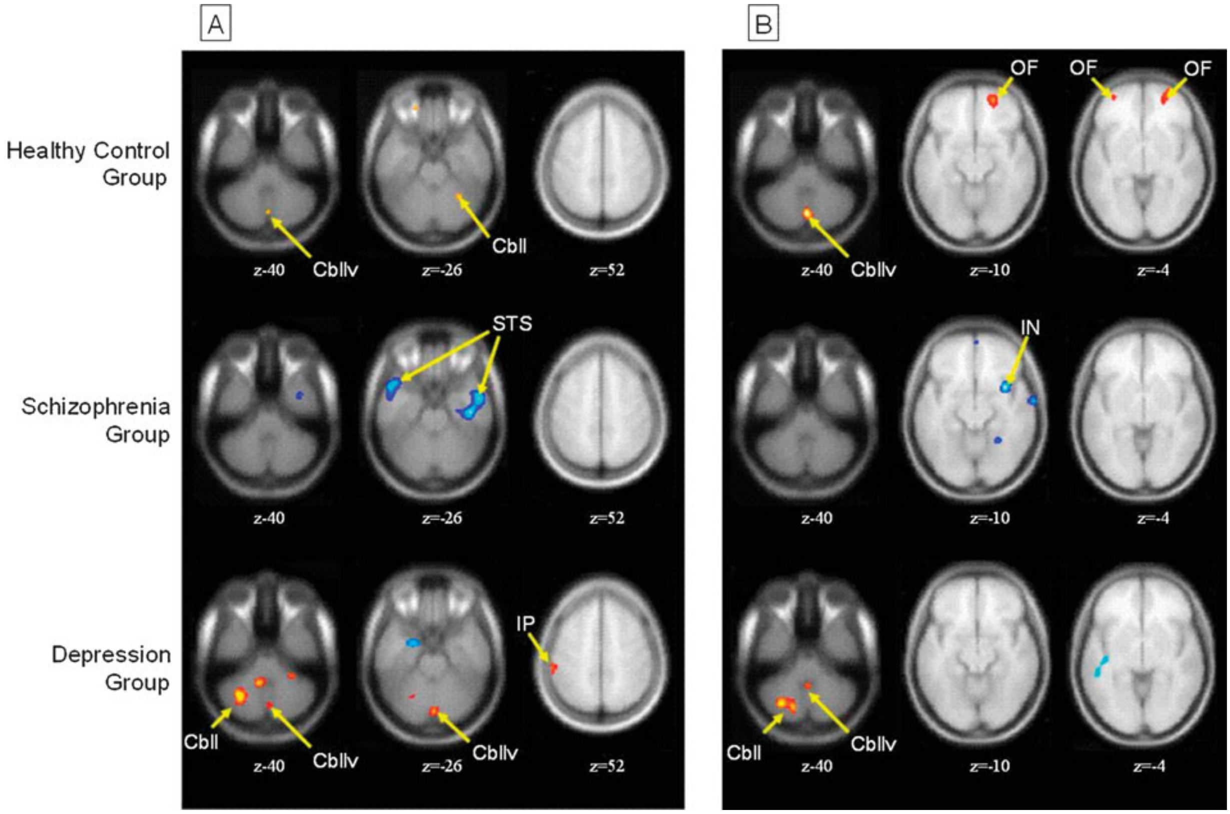

Fig. 3. Within-group analysis for regions activated and deactivated in the non-forced ambivalent condition (A) and forced ambivalent condition (B). Cbllv, cerebellar vermis; Cbll, cerebellum; IN, insula; IP, inferior parietal cortex; OF, orbitofrontal cortex; STS, superior temporal sulcus.

Conflict Resolution in Healthy Participants

Our findings indicated that the left orbitofrontal cortex was recruited to resolve the conflict during evaluative judgment of ambivalent stimuli, regardless of the response condition. Numerous studies support the role of the orbitofrontal cortex in emotional processing and decision making (Bechara, Damasio, & Damasio, 2000; Kringelbach, 2005; Walton, Devlin, & Rushworth, 2004). The orbitofrontal cortex has been proposed to be most likely activated when there is insufficient information available to determine the appropriate response (Elliott, Friston, & Dolan, 2000) and mediate the aspect of subjective experience in emotional processing (Dehaene, Kerszberg, & Changeuz, 1998).

Table 4. Between-group comparison during ambivalent conditions

Region[a]	*F*	Z_{max}	Coordinate (x,y,z)			*Post hoc*[b]
Non-forced ambivalent > univalent						
L. middle frontal gyrus (BA 10)	7.99	3.23	−22	56	10	H > D
L. caudate	12.70	4.21	−14	10	10	H > D, S > D
R. insula	7.60	3.13	30	6	−14	H > S
R. superior temporal sulcus	7.67	3.15	66	−16	−6	D > S
L. middle temporal gyrus (BA 21)	8.62	3.38	−50	−24	−12	S > H
R. cerebellum	7.62	3.14	12	−86	−50	H > S
Forced ambivalent > univalent						
R. orbitofrontal gyrus (BA 11)	7.49	3.11	14	66	−20	H > S
R. superior frontal gyrus (BA 10)	8.23	3.29	24	64	2	H > S, H > D
R. postcentral gyrus (BA 43)	9.96	3.68	68	−8	22	S > H, D >H
R. superior temporal sulcus	7.54	3.12	66	−10	−12	H > S, D > S
L. middle temporal gyrus (BA 21)	10.24	3.74	−48	−24	−10	S > H, S > D
L. precentral gyrus (BA 6)	8.55	3.37	−30	−26	70	S > H, D > H
Cerebellar vermis	7.55	3.12	0	−76	−46	H > D

[a] The threshold of significance was defined as exceeding an uncorrected p level of .001.
[b] We performed *post hoc* t-test between groups. H = healthy control group; S = schizophrenia group; D = depression group.

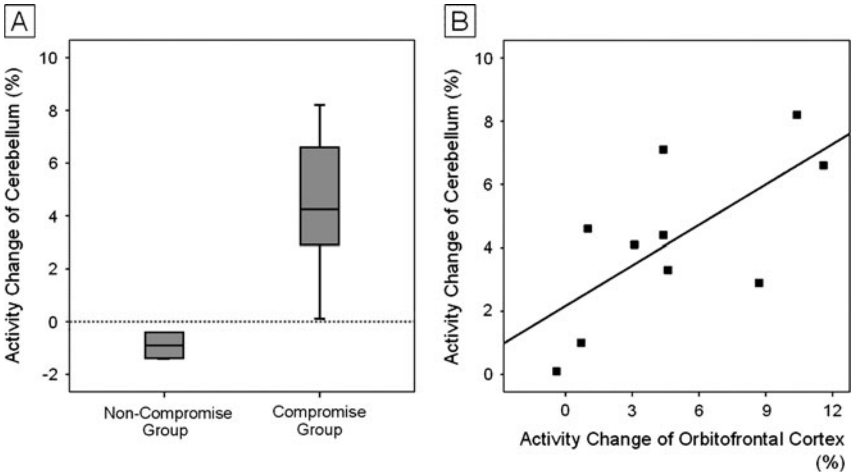

Fig. 4. Correlation between the cerebellum and the orbitofrontal cortex . During non-forced ambivalent, the right cerebellum (x: 30, y: −56, z: −24) demonstrated a dichotomous activation pattern (A). In healthy participants, the right cerebellum was only activated in participants who made compromise responses and was not activated in participants who did not make compromise responses. Among participants who made compromise responses, activity changes of the left orbitofrontal cortex (x: −20, y: 48, z: −26) showed significant correlation with those of the right cerebellum (r = 0.683; *p* = .030; B).

Significant correlations between activity of the left orbitofrontal cortex and the right cerebellum were demonstrated. It is feasible to assume that the orbitofrontal cortex and the cerebellum were involved as a functional unit. However, it must not be overlooked that no direct interconnections between the orbitofrontal cortex and the cerebellum have yet been found and therefore the "prefrontal-cerebellar circuit" usually refers to the lateral prefrontal cortex, not the orbitofrontal cortex (Akkal, Dum, & Stick, 2007; Kelly & Strick, 2003). Although functional connectivity suggests structural connectivity, functional connectivity can exist in the absence of direct, monosynaptic connections and be mediated *via* multisynaptic connections (Greicius et al., 2009). The lateral prefrontal cortex and medial dorsal thalamus were also activated during ambivalent conditions in healthy participants, and we assumed that the functional connectivity pattern between the orbitofrontal cortex and the cerebellum might be mediated *via* the lateral prefrontal cortex or medial dorsal thalamus, which have pronounced connections with the orbitofrontal cortex (Fuster, 1997, Öngür & Price, 2000),

It is interesting to find that the right cerebellum was activated only during the non-forced ambivalent condition, whereas the right prefrontal cortex was activated only during the forced ambivalent condition. Desmond et al. (1998) reported that the cerebellum and the prefrontal cortex have distinct contributions to cognitive processes and suggested that the cerebellum is involved in search, whereas the prefrontal cortex is involved in selection. Our findings strongly support this viewpoint in that the cerebelluar activity, which was activated only in participants who made compromise responses, should reflect the sustained working memory to search for compromise alternatives. Besides, the prefrontal activity seems to be associated with the dichotomous selection between positive or negative during forced ambivalent conditions.

Conflict Resolution and Schizophrenia

The ambivalence-related activity in healthy participants (including the prefrontal cortex, thalamus, and cerebellum) constituted a significant part in the "cognitive dysmetria" hypothesis of schizophrenia (Andreasen et al., 1996), which suggests that the disconnection of the prefrontal-cerebellar circuit is related to abnormal decision making and deficits in emotional evaluation (Sevy et al., 2007; Shad et al., 2006). Especially, the cerebellum is considered a "metron" that monitors the timing of mental and motor activity (Andreasen et al., 1996), and is activated during a wide range of cognitive and motor tasks (Allen, Buxton, Wong, & Courchesne, 1997; Kim et al., 1999). Functional decreases of the cerebellum in schizophrenia have been shown during a variety of cognitively activating conditions (Crespo-Facorro et al., 1999). Consistent with this viewpoint, between-group analyses revealed decreased cerebellar activity in patients with schizophrenia, which should underlie the inability to search and consider compromised responses in non-forced ambivalent situations. Our findings also support the report that schizophrenia patients were impaired in the search condition rather than the select condition (Marvel, Schwartz, & Issacs, 2004).

The orbitofrontal cortex was not activated in patients with schizophrenia; however, other prefrontal activity (BA 6 and BA 10) were recruited for forced ambivalent conditions. Recently, the authors reported volume deficits in the orbitofrontal cortex and orbitofrontal cortex-related thalamic subregion using a connectivity-based parcellation technique, suggesting that a main component of the pathophysiology in schizophrenia may be a cortical-subcortical connectional problem including the orbitofrontal cortex (Kim et al., 2007).

Conflict Resolution and Depression

Although the prefrontal cortex and the cerebellum were activated in patients with depression, the prefrontal activity was weaker and the cerebellar activity was stronger than those of healthy control. One interpretation of cerebellar hyperactivity is that it compensates for decreased prefrontal functions as similarly explained in schizophrenia (Kim et al., 2000). Besides, we gave attention to the inferior parietal activity, which demonstrated correlations with the cerebellar only in the depression group. The inferior parietal lobe is involved in various cognitive functions such as attention, spatial representation, and working memory (Culham & Kanwisher, 2001) and receives projections from the cerebellum *via* the thalamus (Allen et al., 2005; Clower, West, Lynch, & Strick, 2001). Recently, compensatory recruitment of an alternative cortical-subcortical circuit for emotional processing in patients with depression was reported (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). The parietal lobe might have been used by all groups in the task, yet correlations between activity changes within the inferior parietal lobule and those within the cerebellum indicate that parietal-cerebellar connectivity might have been recruited to compensate for the disturbed prefrontal-cerebellar circuit in patients with depression. The alternative recruitment of the parietal-cerebellar circuit should have enabled patients with depression to make use of compromise responses in ambivalent situations. This issue requires study in future research because it is not evident whether the parietal-cerebellar circuit underlies the pathophysiology of depression or simply serves as a "spare tire" for the disturbed prefrontal-cerebellar circuit.

GENERAL CONSIDERATIONS

The results of this study must be addressed within the context of several considerations. The strength of the current study was that PET scans were used as a hemodynamic measurement. If functional magnetic resonance imaging has been used, the main findings in the orbitofrontal cortex would have been prone to dropout and susceptible to artifacts due to its close proximity to the air-filled sinuses (Deichmann, Josephs, Hutton, Corfield, & Truner, 2002; Wilson et al., 2002). A limitation of this study was that we could not completely rule out the potential confounding effect of medications because patients were all medicated with antipsychotics or antidepressants. To examine the effects of antipsychotic medications in patients with schizophrenia, we analyzed behavioral response and brain activity after converting all medications to an equivalent dose of chlorpromazine. However, there was no significant effect of medications on behavioral response and brain activity. We tried to minimize this effect using subtraction analysis, which examined differences between responses to ambivalent and univalent stimuli in each group. Another limitation was that, on average, patients with schizophrenia were above the cutoff for depressive symptoms which should have influenced their performance. There were no significant correlations between depressive symptoms and behavioral responses, but there was a significant correlation between depressive symptoms and ratings of word-stems in patients with schizophrenia.

In summary, the current study began to map the functional neuroanatomy of emotional conflict resolution in ambivalent stimuli. In healthy participants, the prefrontal cortex and the cerebellum play a key role in conflict resolution during evaluative judgment of ambivalent stimuli. The prefrontal cortex activations, which were predominantly activated in forced ambivalent condition, should be associated with the cognitive control to resolve the conflict toward the ambivalent stimuli. The cerebellar activations, which were recruited only in participants who made compromise responses, reflect the sustained working memory to search for compromise alternatives. In patients with schizophrenia, the cerebellum was not activated, which should be linked with the patients' inability to search and consider compromised responses in ambivalent situations. In patients with depression, the functional compensatory recruitment of the parietal-cerebellar circuit was suggested.

ACKNOWLEDGMENT

This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A050495).

REFERENCES

Akkal, D., Dum, R.P., & Stick, P.L. (2007). Supplementary motor area and presupplementary motor area: Targets for basal ganglia and cerebellar output. *Journal of Neuroscience*, *27*, 10659–10673.

Albertson, B., Brehm, J., & Alvarez, R.M. (2004). Ambivalence as experienced conflict. In S. Craig & M.D. Martinez (Ed.), *Ambivalence and the structure of political opinion*. New York: Palgrave Macmillan.

Allen, G., Buxton, R.B., Wong, E.C., & Courchesne, E. (1997). Attentional activation of the cerebellum independent of motor involvement. *Science*, *275*, 1940–1943.

Allen, G., McColl, R., Barnard, H., Ringe, W.K., Fleckenstein, J., & Cullum, C.M. (2005). Magnetic resonance imaging of cerebellar-prefrontal and cerebellar-parietal functional connectivity. *Neuroimage*, *28*, 39–48.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*(4th ed.Text Revision). Washington DC: American Psychiatric Association Press.

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Ponto, L.L., et al. (1996). Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 9985–9990.

Bechara, A., Damasio, H., & Damasio, A.R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex*, *10*, 295–307.

Beck, A.T., & Steer, R.A. (1990). *Beck Anxiety Inventory Manual*. San Antonio, TX: Psychological Corporation.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Beck Depression Inventory Manual* (2nd ed.). San Antonio, TX: Psychological Corporation.

Billig, M., Condor, S., Edwards, D., Gane, M., Middleton, D., & Radley, A. (1988). *Ideological dilemmas: A social psychology of everyday thinking*. London: SAGE.

Bleuler, E. (1950) *Dementia Praecox; or the Group of Schizophrenias*. New York: International University Press.

Buckner, R.L., Petersen, S.E., Ojemann, J.G., Miezin, F.M., Squire, L.R., & Raichle, M.E. (1995). Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience*, *15*, 12–29.

Cacioppo, J.T., Gardner, W.L., & Berntson, G.G. (1999). The affect system has parallel and integrative processing components: Form follows function. *Journal of Personality and Social Psychology*, *76*, 839–855.

Cacioppo, J.T., Gardner, W.L., & Berntson, G.G. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 5497–5502.

Clower, D.M., West, R.A., Lynch, J.C., & Strick, P.L. (2001). The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *Journal of Neuroscience*, *21*, 6283–6291.

Crespo-Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L., et al. (1999). Recalling word lists reveals "cognitive dysmetria" in schizophrenia: A positron emission tomography study. *American Journal of Psychiatry*, *156*, 386–392.

Culham, J.C., & Kanwisher, N.G. (2001). Neuroimaging of cognitive functions in human parietal cortex. *Current Opinion in Neurobiology*, *11*, 157–163.

Cunningham, W.A., Johnson, M.K., Gatenby, J.C., Gore, J.C., & Banaji, M.R. (2003). Neural components of social evaluation. *Journal of Personality and Social Psychology*, *85*, 639–649.

Danion, J.M., Kauffmann-Muller, F., Grangé, D., Zimmermann, M.A., & Greth, P. (1995). Affective valence of words, explicit and implicit memory in clinical depression. *Journal of Affective disorders*, *34*, 227–234.

Dehaene, S., Kerszberg, M., & Changeuz, J.P. (1998). A neuronal model of global workspace in effortful cognitive tasks. *Proceedings of the National Academy of Sciences of the United States of America*, *95*, 14529–14534.

Deichmann, R., Josephs, O., Hutton, C., Corfield, D.R., & Turner, R. (2002). Compensation of susceptibility-induced BOLD sensitivity losses in echo-planar fMRI imaging. *Neuroimage*, *15*, 120–135.

Desmond, J.E., Gabrieli, J.D., & Glover, G.H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: Evidence for a distinction between selection and search. *Neuroimage*, *7*, 368–376.

Elliott, R., Friston, K.J., & Dolan, R.J. (2000). Dissociable neural responses in human reward systems. *Journal of Neuroscience*, *20*, 659–6165.

Freud, S. (1917). *Mourning and melancholia* (14th ed.). London: Vintage.

Fuster, J.M. (1997). *The prefrontal cortex*. New York: Raven.

Greicius, M.D., Supekar, K., Menon, V., & Dougherty, R.F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, *19*, 72–78.

Ito, T.A., Larsen, J.T., Smith, N.K., & Cacioppo, J.T. (1998). Negative information weighs more heavily on the brain: The negative bias in evaluative categorizations. *Journal of Personality and Social Psychology*, *75*, 887–900.

Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., & Davidson, R.J. (2007). Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *Journal of Neuroscience*, *27*, 8877–8884.

Jung, Y.C., An, S.K., Seok, J.H., Kim, J.S., Oh, S.J., Moon, D.H., et al. (2006). Neural substrates associated with evaluative processing during co-activation of positivity and negativity: A PET investigation. *Biological Psychology*, *73*, 253–261.

Jung, Y.C., Park, H.J., Kim, J.J., Chun, J.W., Kim, H.S., Kim, N.W., et al. (2008). Reciprocal activation of the orbitofrontal cortex and ventrolateral prefrontal cortex in processing ambivalent stimuli. *Brain Research*, *1246*, 136–143.

Kay, S.R. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–267.

Keightley, M.L., Winocur, G., Graham, S.J., Mayberg, H.S., Hevenor, S.J., & Grady, C.L. (2003). An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia*, *41*, 585–596.

Kelly, R.M., & Strick, P.L. (2003). Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *Journal of Neuroscience*, *23*, 8432–8444.

Kim, J.J., Andreasen, N.C., O'Leary, D.S., Wiser, A.K., Ponto, L.L.B., Watkins, G.L., et al. (1999). Direct comparison of the neural substrates of recognition memory for words and faces. *Brain*, *122*, 1069–1083.

Kim, J.J., Kim, D.J., Kim, T.G., Seok, J.H., Chun, J.W., Oh, M.K., et al. (2007). Volumetric abnormalities in connectivity-based subregions of the thalamus in patients with chronic schizophrenia. *Schizophrenia Research*, *97*, 226–235.

Kim, J.J., Mohamed, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L., et al. (2000). Regional neural dysfunctions in chronic schizophrenia studied with positron emission tomography. *American Journal of Psychiatry*, *157*, 542–548.

Kim, J.J., Seok, J.H., Park, H.J., Lee, S.D., Lee, M.C., & Kwon, J.S. (2005). Functional disconnection of the semantic networks in schizophrenia. *Neuroreport*, *16*, 355–359.

Kringelbach, M.L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. *Nature Reviews Neuroscience*, *6*, 691–702.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (1998). *International Affective Picture System (IAPS): Photographic slides*. Gainesville: Center for Research in Psychophysiology University of Florida.

Linehan, M.M. (1993). *Cognitive-behavioral treatment of borderline personality disorders*. New York: Guilford Press.

Marvel, C.L., Schwartz, B.L., & Issacs, K.L. (2004). Word production deficits in schizophrenia. *Brain and Language 89*, 182–191.

Mitchell, D.G., Nakic, M., Fridberg, D., Kamel, N., Pine, D.S., & Blair, R.J. (2007). The impact of processing load on emotion. *Neuroimage*, *34*, 1299–1309.

Norman, W.H., Miller, I.W., & Dow, M.G. (1988). Characteristics of depressed patients with elevated levels of dysfunctional cognitions. *Cognitive Therapy and Research*, *12*, 39–52.

Öngür, D., & Price, J.L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, *10*, 206–219.

Peeters, G., & Czapinski, J. (1990). Positive-negative asymmetry in evaluations: The distinction between affective and informational negativity effects. In W. Stroebe & M. Hewstone (Eds.), *European review of social psychology*. New York: Wiley.

Raulin, M.L., & Brenner, V. (1993). Ambivalence. In C.G. Costello (Ed.), *Symptoms of schizophrenia*. New York: Wiley.

Seok, J.H., An, S.K., Lee, E., Lee, H.S., Lee, Y.J., Jeon, J.H., et al. (2006). Behavioral evidence of blunted and inappropriate affective responses in schizophrenia: Lack of a 'negativity bias'. *Psychiatry Research*, *142*, 53–66.

Sevy, S., Burdick, K.E., Visweswaraiah, H., Abdelmessih, S., Lukin, M., Yechiam, E., et al. (2007). Iowa Gambling Task in schizophrenia: A review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophrenia Research*, *92*, 74–84.

Shad, M.U., Muddasani, S., & Keshavan, M.S. (2006). Prefrontal subregions and dimensions of insight in first-episode schizophrenia–a pilot study. *Psychiatry Research*, *146*, 35–42.

Sincoff, J.B. (1992). Ambivalence and defense: Effects of a repressive style on normal adolescents' and young adults mixed feelings. *Journal of Abnormal Psychology*, *101*, 251–256.

Talairach, J., & Tournoux, P. (1988). *Coplanar stereotactic atlas of the human brain*. Stuttgart: Thieme.

van Veen, V., & Carter, C.S. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, *14*, 593–602.

Walton, M.E., Devlin, J.T., & Rushworth, M.F. (2004). Interactions between decision making and performance monitoring within prefrontal cortex. *Nature Neuroscience*, *7*, 1259–1265.

Wilson, J.L., Jenkinson, M., de Araujo, I., Kringelbach, M.L., Rolls, E.T., & Jezzard, P. (2002). Fast, fully automated global and local magnetic field optimization for fMRI of the human brain. *Neuroimage*, *17*, 967–976.

APPENDIX

Table A. Comparison of mean valence score[a] of stimuli materials

	Healthy	Schizophrenia	Depression	F	p
Positive disyllabic words	4.3 (0.4)	4.6 (0.4)	3.8 (0.9)	5.363	0.010
Negative disyllabic words	1.5 (0.2)	1.4 (0.5)	1.7 (0.5)	1.540	0.229
Monosyllabic word-stem	3.3 (0.4)	3.3 (0.4)	2.9 (0.3)	6.669	0.004

[a] Before performing the task, the valence of all disyllabic words and monosyllabic word-stems was determined using a 5-point Likert scale: 1 (strong negative), 2 (weak negative), 3 (neutral), 4 (weak positive), and 5 (strong positive).