were recognized cross-culturally (Sauter et al., 2010). Our present result is similar to the findings of this previous study. Further, in accordance with our results, recent studies of facial expression have shown that happy facial expression is not cross-culturally different between Caucasian and Asian participants (Shioiri et al., 1999; Jack et al., 2009, 2012). Our results suggest that the happy emotion is universal in vocal recognition as well as facial recognition. On the other hand, in the vocal recognition, other positive emotions such as Pleasure can show culture-specific biases.

#### CROSS-CULTURAL EFFECT FOR NEGATIVE EMOTION

Correct rejection rates (validity) of Anger, Pain, Sadness and Surprise were not significantly different between Caucasian and Japanese subjects (**Table 2**). These findings suggest that these two items are valid beyond the culture. On the other hand, correct rejection rates of Disgust and Fear were significantly different between Caucasian and Japanese subjects (**Table 2**). These findings indicate that it is very difficult for Japanese to identify these two emotions when they listened to MAV.

A recent cross-cultural study between Western participants and Namibian participants suggested that primary basic negative emotions such as Anger, Disgust, Fear, Sadness, and Surprise can be recognized in both cultures (Sauter et al., 2010). We predicted that ratings of negative emotion are culturally universal. However, our results did not accord with that previous study, and we also observed cross-cultural differences in the recognition of Anger, Disgust, and Fear. **Figure 1** and **Table 1** show that Intensity ratings for angry, disgusted, fearful, and surprised vocalizations were significantly higher in the Canadian Group than in the Japanese Group. Valence ratings were higher in Japanese than in Canadians regarding some negative emotions (i.e., anger, disgust, and fear). These differences are consistent as higher perceived Intensity of a negative emotion is typically associated with lower (more negative) perceived Valence. These findings could reflect cross-cultural features of Intensity and Valence in negative emotion. Previous studies of facial expression have demonstrated that cross-cultural differences exist in the recognition of angry, disgusted, and fearful face (Shioiri et al., 1999; Jack et al., 2012). In agreement with these results, the recognition of Anger, Disgust, and Fear may reflect cross-cultural differences between Caucasian and Asian participants. On the other hand, the recognition of sad vocalizations (cries) was not significantly different, in agreement with Sauter et al. (2010). Previous studies of facial expression have shown cross-cultural differences in the recognition of sad expressions (Shioiri et al., 1999; Jack et al., 2012). This finding could reflect the fact that the recognition of sad vocalization could be more similar across cultures in comparison with the facial recognition. A previous study indicated that Japanese are severely affected by the meaning of words in recognition of Japanese emotions (Kitayama and Ishii, 2002). The other reason why Japanese find it difficult to differentiate negative emotional vocalizations may be that Japanese need more contextual information to recognize emotions than Canadians.

Concerning of ratings of negative vocalizations, **Table 2** shows that hit rates (accuracy) and specificity were lower in Japanese participants than in Canadian participants for ratings of angry, disgusted, fearful, and painful vocalizations. Especially, the strongest pattern of confusion was observed between fearful and surprised vocalizations in Japanese participants. This pattern is a typical pattern of confusion in Caucasian listeners as well (Belin et al., 2008). For both Japanese and Canadian participants, when listening to fearful vocalizations, the Intensity ratings for Surprise were high (Canadian: fearful $68 \pm 2.5$ vs. surprised $57 \pm 3.0$; Japanese: fearful $54 \pm 5.9$ vs. surprised $66 \pm 5.2$). These results suggest that it was difficult for Japanese participants to discriminate between fearful and surprised vocalizations. The hit rate of fearful vocalizations in Japanese participants was significantly lower than that in Canadian participants. In contrast, the hit rate of surprised vocalizations was not significantly different between Japanese and Canadian. This finding suggests that Japanese tend to be difficult to identify emotional intensity of fearful vocalizations from MAV.

A recent cross-cultural study between Japanese and Dutch participants demonstrated congruency effects displayed by happy face/voice and angry face/voice (Tanaka et al., 2010). This study indicated that, while listening to Anger voices by Dutch speakers, accuracy ratings of Japanese participants are significantly lower than Dutch participants. In agreement with this result, our study showed that ratings for angry vocalizations showed significantly less Intensity and less negative Valence in Japanese than in Canadian listeners.

#### THE EFFECTS OF PARTICIPANT'S AND ACTOR'S GENDER IN JAPANESE

Our present study has demonstrated a significant gender effect by actor in accordance with a previous Canadian study (Belin et al., 2008), and hit rates for female vocalizations are higher than for male vocalizations (**Figure 2**). In general, women are believed to be more emotionally expressive than are men (Fischer, 1993). A previous study of facial recognition also revealed that females had a higher rate of correct classification in comparison with males (Thayer and Johnsen, 2000). Our results suggest that Japanese as well as Canadians are also more accurate at recognizing female vocalizations.

A previous study demonstrated an effect of listener's gender in Canadian participants (Belin et al., 2008). In line with the previous study, in the analysis including Japanese and Canadian participants, the effect of participant's gender was replicated.

Our present study has at least two important limitations. First, stimuli consisted of acted vocalizations, not genuine expressions of emotion. Ideally, research on emotional perception would only use naturalistic stimuli. However, collecting genuine emotional expressions across different actors in comparable settings and for different emotions is very difficult and presents ethical problems. Second, in the present study, cross-cultural differences between Canadian and Japanese listeners were confirmed in the recognition of some emotional vocalizations. In the future, it will be necessary to develop a set of stimuli to increase cross-cultural validity.

In summary, we tested for cross-cultural differences between Japanese and Canadian listeners in perception of non-verbal affective vocalization using MAVs. Significant Group × Emotion interactions were observed for all ratings of Intensity, Valence, and Arousal in comparison with Japanese and Canadian participants of our present study. Although ratings did not differ across cultural groups for Pain, Surprise, and Happiness, they markedly differed for the angry, disgusted, and fearful vocalizations which were rated

by Japanese listeners as significantly less intense and less negative than by Canadian listeners; similarly, pleased vocalizations were rated as less intense and less positive by Japanese listeners. These results suggest, in line with Sauter et al. (2010), that there were cross-cultural differences in the perception of emotions through non-verbal vocalizations, and our findings further suggest that these differences are not necessarily only observed for positive emotions.

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*Regular Article*

# Relationships between exploratory eye movement dysfunction and clinical symptoms in schizophrenia

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*Aim:* Many psychophysiological tests have been widely researched in the search for a biological marker of schizophrenia. The exploratory eye movement (EEM) test involves the monitoring of eye movements while subjects freely view geometric figures. Suzuki *et al.* (2009) performed discriminant analysis between schizophrenia and non-schizophrenia subjects using EEM test data; consequently, clinically diagnosed schizophrenia patients were identified as having schizophrenia with high probability (73.3%). The aim of the present study was to investigate the characteristics of schizophrenia patients who were identified as having schizophrenia on EEM discriminant analysis (SPDSE) or schizophrenia patients who were identified as not having schizophrenia on EEM discriminant analysis (SPDNSE).

*Methods:* The data for the 251 schizophrenia subjects used in the previous discriminant-analytic study were analyzed, and the demographic or symptomatic characteristics of SPDSE and SPDNSE were investigated. As for the symptomatic features, a factor analysis of the Brief Psychiatric Rating Scale (BPRS) rating from the schizophrenia subjects was carried out.

*Results:* Five factors were found for schizophrenia symptoms: excitement/hostility; negative symptoms; depression/anxiety; positive symptoms; and disorganization. SPDSE had significantly higher factor scores for excitement/hostility, negative symptoms and disorganization than SPDNSE. Furthermore, the BPRS total score for the SPDSE was significantly higher than that for the SPDNSE.

*Conclusion:* SPDSE may be a disease subtype of schizophrenia with severe symptoms related to excitement/hostility, negative symptoms and disorganization, and EEM parameters may detect this subtype. Therefore, the EEM test may be one of the contributors to the simplification of the heterogeneity of schizophrenia.

**Key words:** biological marker, clinical symptoms of schizophrenia, exploratory eye movement, heterogeneity, schizophrenia.

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MANY PSYCHOPHYSIOLOGICAL TESTS have been performed in the search for a biological marker for schizophrenia.[1,2] Event-related potentials (ERP), P300,[3] P50[4] and mismatch negativity (MMN),[5,6] prepulse inhibition (PPI),[7,8] saccadic and smooth pursuit eye movements[9–12] and working memory tasks[13,14] have been widely researched. Moreover, many researchers have focused on abnormalities of working memory as an endophenotype for schizophrenia in molecular genetic studies.[15,16]

We have studied eye movements while subjects freely viewed geometric figures; this is called the exploratory eye movement (EEM) test. In most previous studies, only schizophrenia patients have consistently shown disturbances of EEM.[17–25] Moreover, the parents and siblings of schizophrenia patients had EEM dysfunctions.[26,27] In addition, EEM demonstrated a significant linkage to chromosome 22q11.[28] Chromosome 22q11 is one of the most interesting regions in the genetic etiology of schizophrenia. Microdeletions at chromosome 22q11 cause velocardio-facial syndrome (VCFS/DiGeorage syndrome: DGS), and patients with VCFS have a high risk of schizophrenia.[29,30] Furthermore, there is strong evidence that this deletion is a risk factor for schizophrenia in a genome-wide association study (GWAS) using copy number variants (CNV).[31] Therefore, we believe that EEM disturbance may be a biological marker of schizophrenia, in addition to the aforementioned physiological defects.

On the basis of these findings, we considered that the EEM test might be useful for the clinical diagnosis of schizophrenia as well. Suzuki *et al.* carried out a discriminant analysis between schizophrenia patients and non-schizophrenia subjects in a large sample using EEM test data.[32] EEM performance was recorded in 251 schizophrenia patients and 389 non-schizophrenia subjects (111 patients with mood disorder; 28 patients with neurotic disorder; 250 normal controls). As a result, 184 of the 251 clinically diagnosed schizophrenia patients were identified as having schizophrenia (sensitivity, 73.3%); and 308 of the 389 clinically diagnosed non-schizophrenia subjects were identified as non-schizophrenic (specificity, 79.2%). Based on this finding, we propose that the EEM test might be useful for the clinical diagnosis of schizophrenia.

In the discriminant-analytic study,[32] we were interested in characteristics of the schizophrenia patients who were identified as having schizophrenia on EEM discriminant analysis (SPDSE), or those who were identified as not having schizophrenia on EEM discriminant analysis (SPDNSE). Many researchers have indicated the potential heterogeneity of schizophrenia.[33–37] Hence, the EEM parameters may be able to detect different subtypes of schizophrenia. In the present study, to clarify the features of SPDSE and SPDNSE, we reanalyzed that data,[32] and focused on the demographic or symptomatic characteristics. If the characteristics of SPDSE and SPDNSE are clarified, further knowledge regarding the heterogeneity of schizophrenia may be yielded. Therefore, in the present study we discuss the features of SPDSE and SPDNSE and a further application of EEM for scientific research into schizophrenia.

## METHODS

### Subjects

Two hundred and fifty-one schizophrenia patients participated in the discriminant-analytic study (paranoid type, 65.3%; hebephrenic type, 15.9%; catatonic type, 1.2%; undifferentiated type, 5.2%; residual type, 9.6%; simple type, 1.6%; and unspecified type, 1.2%).[32] The patients were in/outpatients recruited from multiple centers, eight university hospitals and three affiliated hospitals. Diagnoses were made by one experienced psychiatrist according to the ICD-10 criteria for research at each university or hospital.[38] The demographic characteristics of the subjects were as follows: age, 37.9 ± 11.3 years; gender (M/F), 157/94; and duration of illness, 14.5 ± 13.1 years. The patients who had a history of alcohol abuse or illicit substance abuse, or head injury were excluded from the study; also excluded were those with convulsive, neurologic or ophthalmologic disorders.

The clinical symptoms of the schizophrenia patients were assessed using the Brief Psychiatric Rating Scale (BPRS),[39] which yielded an average total score of 41.5 ± 13.3. All BPRS ratings were done by one experienced psychiatrist in each university or hospital. Of the 251 patients with schizophrenia, 249 received neuroleptic medication. The average daily dosage is expressed as a haloperidol equivalent of 13.9 ± 10.7 mg.[40] This study was approved by the Ethics Committees of the eight universities. Written informed consent was obtained from all participants, after the procedures and possible risks of the study were fully explained.

## Procedure

A standard test of the EEM using a digital eye-mark recording system (nac Image Technology, EMR-NS, Tokyo, Japan) was performed. An eye camera that detected corneal reflection of infrared light to identify eye movements, and a 15-in LCD monitor (1024 × 768 pixels) that displayed target figures for the EEM tasks (Fig. 1) were included in this system. According to the following method, three horizontal S-shaped figures (an original target figure and two figures slightly different from the original target figure) were individually displayed on the LCD monitor (Fig. 1). First, the retention task: the subject was shown the original S-shaped figure (Fig. 1a) for 15 s. Next, the comparison task: the subject was instructed to compare a figure with the original figure (Fig. 1a); they were then shown a figure slightly different from the original one, which had one bump in a different position (Fig. 1b), for 15 s. After 15 s had elapsed and with the figure still in view, the subject was asked whether it differed from the original figure and, if it did, how it differed. After the subject had replied and while the figure was still being shown, he/she was asked 'Are there any other differences?' The comparison task was then repeated with a figure without bumps (Fig. 1c).

In the digital eye-mark recording system, the detected eye movements were automatically analyzed by a digital computerized EEM analyzer. Consequently, four parameters emerged: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL) and responsive search score (RSS). The NEF, TESL and MESL were based on data of eye movements that occurred during 15 s of the retention task. In the comparison task, the RSS was based on data of eye movements that occurred for 5 s immediately after the question: 'Are there any other differences?' More detailed descriptions of the EEM test equipment and method are given in our previous studies.[17,20,32]

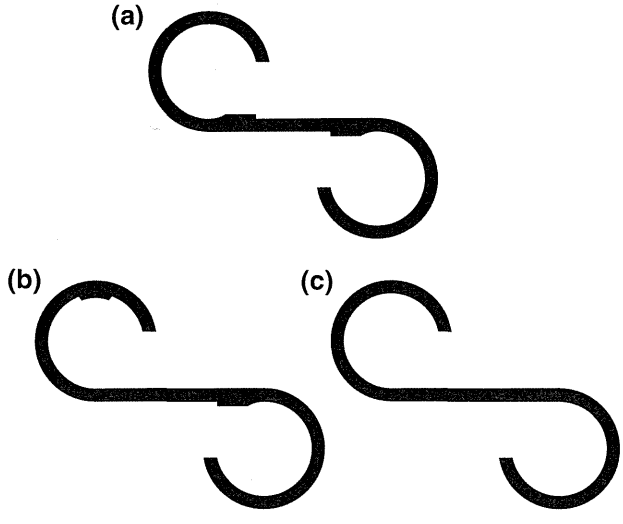


**Figure 1.** (a) Original target figure; (b,c) two figures slightly different from the target.

In our previous study, 184 of the 251 clinically diagnosed schizophrenia patients were identified as having schizophrenia on discriminant analysis using the EEM parameters (SPDSE).[32] The remaining 67 schizophrenia patients were identified as not having schizophrenia (SPDNSE). Table 1 lists the background data of the SPDSE and SPDNSE. In the present study we compared demographic and symptomatic characteristics of SPDSE with those of SPDNSE.

## Statistical analysis

Group differences on the demographic and symptomatic data were assessed using the *t*-test or the $\chi^2$ test. For group comparison of the symptomatic data, scores for factors extracted by factor analysis of BPRS ratings and BPRS total scores were used. In the factor analysis, we conducted a principal component analysis with orthogonal rotation (Varimax method) according to previous studies.[41–43] Moreover, based on prior studies, factors with eigenvalues >1.0 were considered to be meaningful.[41,43] All statistical analyses were performed using SPSS for Windows version 17.0. The statistical significance was set at $P < 0.05$ (two-tailed).

# RESULTS

## Group comparisons (SPDSE vs SPDNSE) of demographic characteristics

There were no significant differences for age, sex, duration of illness or drug dosage between SPDSE and SPDNSE.

## Group comparisons (SPDSE vs SPDNSE) of subtypes and clinical symptoms

There were no significant differences for the subtypes between SPDSE and SPDNSE.

**Table 1.** Subject characteristics

| | SPDSE ($n = 184$) | SPDNSE ($n = 67$) |
|---|---|---|
| Age (years), mean ± SD | 38.0 ± 12.6 | 37.7 ± 12.0 |
| Gender (M/F) | 112/72 | 45/22 |
| Duration of illness (years), mean ± SD | 14.6 ± 13.9 | 14.3 ± 10.8 |
| Equivalent dose of haloperidol (mg), mean ± SD[†] | 14.4 ± 11.1 | 12.5 ± 9.7 |
| Subtype, *n* (%) | | |
| Paranoid | 120 (65.3) | 44 (65.6) |
| Hebephrenic | 30 (16.3) | 10 (14.9) |
| Catatonic | 3 (1.6) | 0 (0) |
| Undifferentiated | 9 (4.9) | 4 (6.0) |
| Residual | 18 (9.8) | 6 (9.0) |
| Simple | 3 (1.6) | 1 (1.5) |
| Unspecified | 1 (0.5) | 2 (3.0) |

[†]In each group (SPDSE or SPDNSE), one patient did not receive neuroleptic medication, respectively.
SPDSE, schizophrenia patients identified as having schizophrenia on exploratory eye movement (EEM) discriminant analysis; SPDNSE, schizophrenia patients identified as not having schizophrenia on EEM discriminant analysis.

## Factor analysis of BPRS items

Table 2 lists the factors and factor loadings derived using principal component analysis of BPRS rating. The principal component analysis extracted five factors that accounted for 70.0% of the variance. Based on previous studies, BPRS items with factor loadings >0.5 were considered to load on the

**Table 2.** Factors and factor loadings derived in BPRS principal component analysis

| | Factor | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| BPRS items | | | | | |
| Somatic concern | 0.033 | 0.080 | 0.615 | 0.505 | −0.074 |
| Anxiety | 0.184 | 0.123 | 0.727 | 0.272 | −0.126 |
| Emotional withdrawal | 0.070 | 0.879 | 0.139 | 0.043 | 0.140 |
| Conceptual disorganization | 0.401 | 0.298 | 0.113 | 0.356 | 0.629 |
| Guilt feelings | 0.091 | −0.085 | 0.670 | −0.157 | 0.487 |
| Tension | 0.416 | 0.404 | 0.543 | 0.106 | −0.126 |
| Mannerisms and posturing | 0.383 | 0.457 | 0.178 | 0.339 | 0.393 |
| Grandiosity | 0.736 | −0.115 | 0.133 | 0.124 | 0.158 |
| Depressive mood | 0.192 | 0.287 | 0.722 | 0.041 | −0.058 |
| Hostility | 0.783 | 0.077 | 0.213 | 0.210 | −0.118 |
| Suspiciousness | 0.477 | 0.126 | 0.273 | 0.546 | −0.111 |
| Hallucinatory behavior | 0.246 | 0.171 | 0.045 | 0.805 | 0.067 |
| Motor retardation | 0.004 | 0.850 | 0.179 | 0.159 | 0.083 |
| Uncooperativeness | 0.677 | 0.432 | −0.057 | 0.122 | 0.086 |
| Unusual thought content | 0.276 | 0.170 | 0.133 | 0.734 | 0.322 |
| Blunted affect | 0.021 | 0.857 | 0.083 | 0.168 | 0.160 |
| Excitement | 0.778 | −0.023 | 0.195 | 0.218 | 0.153 |
| Disorientation | −0.034 | 0.241 | −0.241 | 0.056 | 0.659 |
| Variance explained (total = 70.0%)[†] | 17.5 | 17.5 | 14.1 | 12.6 | 8.4 |

[†]Cumulative or percentage of variance explained is rounded off; therefore, the cumulative percentage is not identical to the sum of each percentage. Underline, BPRS items with factor loadings >0.5.
BPRS, Brief Psychiatric Rating Scale.

**Table 3.** Mean factor scores and BPRS total score (mean ± SD)

| | SPDSE ($n = 184$) | SPDNSE ($n = 67$) | $t$ (d.f. = 249) | $z$ |
|---|---|---|---|---|
| Factor | | | | |
| 1 Excitement/hostility | 0.09 ± 1.07 | −0.25 ± 0.74 | | −2.16* |
| 2 Negative symptoms | 0.10 ± 1.01 | −0.27 ± 0.93 | −2.57* | |
| 3 Depression/anxiety | −0.03 ± 1.03 | 0.07 ± 0.92 | 0.70 | |
| 4 Positive symptoms | 0.03 ± 1.03 | −0.07 ± 0.92 | −0.71 | |
| 5 Disorganization | 0.08 ± 1.03 | −0.21 ± 0.89 | −2.06* | |
| BPRS total score (mean ± SD) | 43.08 ± 13.48 | 37.51 ± 12.10 | −2.98* | |

*$P < 0.05$.

BPRS, Brief Psychiatric Rating Scale; SPDSE, schizophrenia patients identified as having schizophrenia on exploratory eye movement (EEM) discriminant analysis; SPDNSE, schizophrenia patients identified as not having schizophrenia on EEM discriminant analysis.

respective factor.[41,43] Consequently, we summarized the five factors as follows: factor 1 loaded heavily in grandiosity, hostility, uncooperativeness and excitement; factor 2 had heavy loadings in emotional withdrawal, motor retardation and blunted affect; factor 3 loaded heavily in somatic concern, anxiety, guilt feelings, tension and depressive mood; factor 4 had heavy loadings in somatic concern, suspiciousness, hallucinatory behavior and unusual thought content; factor 5 loaded heavily in conceptual disorganization and disorientation. Accordingly, we interpreted the five factors as having the following dimensions: factor 1, excitement/hostility (17.5% of total variance); factor 2, negative symptoms (17.5%); factor 3, depression/anxiety (14.1%); factor 4, positive symptoms (12.6%); and factor 5, disorganization (8.4%).

### Group comparisons (SPDSE vs SPDNSE) of factor scores

Table 3 lists the mean factor scores of the five factors for SPDSE and SPDNSE. SPDSE had significantly higher scores of excitement/hostility ($P = 0.005$), negative symptoms ($P = 0.011$) and disorganization ($P = 0.040$) than SPDNSE. Furthermore, the BPRS total score of SPDSE was significantly higher than that of the SPDNSE ($P = 0.003$). For the excitement/hostility factor, the Levene test for equality of variance did not show homoskedasticity between the two groups. Therefore, the $P$-value for the excitement/hostility factor was based on an unequal-variance $t$-value. In order to confirm the result of the excitement/hostility factor, we also performed the non-parametric test, Mann–Whitney $U$-test. Consequently, SPDSE also demonstrated significantly higher scores of excitement/hostility than SPDNSE on non-parametric analysis ($P = 0.031$).

## DISCUSSION

Suzuki *et al.* performed discriminant analysis between schizophrenia patients and non-schizophrenia subjects using the EEM test data.[32] As a result, 184 of the 251 clinically diagnosed schizophrenia patients were identified as having schizophrenia (sensitivity, 73.3%). In the present study, results of the factor analysis of BPRS ratings from the aforementioned 251 schizophrenia subjects produced five factors of symptoms (excitement/hostility; negative symptoms; depression/anxiety; positive symptoms; and disorganization). Excitement/hostility, negative symptoms and disorganization were more predominant in the 184 SPDSE subjects compared to the SPDNSE subjects. Furthermore, the BPRS total score of the SPDSE was significantly higher than that of the SPDNSE. Consequently, the SPDSE group may consist of patients with severe schizophrenia, and the severity of symptoms in SPDSE was found to be due mainly to excitement/hostility, negative symptoms and disorganization.

Evidence for five dimensions in schizophrenia symptoms was found in the present study. Many studies have proposed similar five-factor structures.[41–47] In these studies, the Positive and Negative Syndrome Scale (PANSS) has been used as the symptom rating scale. In contrast, the present data were based on the BPRS. All items of the BPRS, however, are included in the PANSS.[39,48] Therefore, it

is possible that the present findings reflect the past studies of the factor analysis using PANSS items. Consequently, although items included for each factor in previous studies and the present study were not identical, the present findings of the factor analysis are distinctly similar to previous factor-analytic study results. Thus, we consider that the present five-factor structure may be meaningful for the symptomatology of schizophrenia. The PANSS, however, is more informative than the BPRS, therefore the present study may be limited by this issue.

In the present study, demographic data, age, sex, duration of illness and drug dosage for SPDSE and SPDNSE were not significantly different. But there were significant differences for symptom, excitement/hostility, negative symptoms and disorganization between SPDSE and SPDNSE. In our previous study, EEM parameters were not influenced by the demographic data.[27,32] Moreover, one of the EEM parameter, RSS, which was principally used in the discriminant analysis of SPDSE, was associated with negative symptoms.[17] Altogether, we believe that differences between SPDSE and SPDNSE in the EEM may relate to symptoms of schizophrenia, but not demographic data, sex, age, course of illness or medication.

With regard to the ICD-10 subtypes, we also did not find significant differences between SPDSE and SPDNSE. This finding seems to conflict with the significant differences of the BPRS scores between the two groups. Lykouras *et al.* investigated relationships between the DSM-III-R schizophrenia subtypes and the PANSS scores.[49] As a result, paranoid type was associated with positive symptoms, and disorganized type linked to negative symptoms. In addition to disorganized type, however, catatonic type related to negative symptoms. Moreover, based on the DSM-IV-TR, the schizophrenia symptoms have been divided into three dimensions.[50] However, past reports and the present study propose that schizophrenia may be symptomatically more complex.[41–47] This has also been indicated by Wolthaus *et al.*[47] In this way, subtypes and dimensions of the diagnostic criteria are often not consistent with those of the symptomatic rating scales. There is, however, a possible limitation to the present study. Although we discussed diagnoses using the ICD-10 criteria and the BPRS scores in detail, inter-rater and intra-rater reliabilities for those were not formally assigned. Consequently, if they were formally assigned, the ICD-10 subtypes might coincide with the BPRS scores.

Based on the present findings, SPDSE may be associated with excitement/hostility, negative symptoms and disorganization in the present five symptomatic dimensions. Accordingly, SPDSE may have three different dimensions; but it can also be said that SPDSE may be a schizophrenia subtype characterized by these three dimensions. The present findings may indicate that there is a putative subtype of schizophrenia with severe symptoms related to excitement/hostility, negative symptoms and disorganization. Furthermore, the EEM abnormality may be a biological marker for this subtype of schizophrenia. There is another point worth making. As mentioned here, the EEM parameter, RSS was associated with negative symptoms.[17] Thus, negative symptoms may be the most specific of the three dimensions to the subtype.

In addition to the schizophrenia patients, their parents and siblings also had EEM dysfunction.[26,27] Therefore, we considered that the EEM abnormality may be an intermediate phenotype of schizophrenia, and may be useful for linkage studies of schizophrenia. Indeed, we found a significant linkage to chromosome 22q11.2–12.1 in our previous linkage study using EEM impairment as an endophenotype of schizophrenia.[28] Chromosome 22q11 is one of the most interesting regions for the etiology of schizophrenia. Moreover, in this area, there are several candidate genes for schizophrenia, for example COMT, PRODH and ZDHHC8, and so on.[29,30]

Many researchers have presented positive linkage and association findings with schizophrenia, but initial findings have often not been replicated.[30] One of the most significant causes of conflicting results in the present molecular genetic studies of schizophrenia may be the potential heterogeneity of schizophrenia. Several investigators have suggested that schizophrenia is not a single disease entity but may reflect common symptomatology caused by several distinct genetic abnormalities.[33–37] As mentioned here, the EEM deficits are linked to chromosome 22q11. If the EEM parameters are associated with a schizophrenia subtype with severe symptoms related to excitement/hostility, negative symptoms and disorganization, chromosome 22q11 and genes of 22q11 may relate to this subtype. In this manner, if we are able to find a new subtype using the EEM disturbances, and clarify the heterogeneity of schizophrenia, then linkage or association studies for schizophrenia using the subtype may yield further knowledge regarding the genetic influences on schizophrenia.

In conclusion, we have found evidence for the existence of five dimensions of schizophrenia symptoms: excitement/hostility; negative symptoms; depression/anxiety; positive symptoms; and disorganization. Schizophrenia patients with EEM abnormalities (SPDSE) may have severe symptoms related to excitement/hostility, negative symptoms and disorganization. In light of the heterogeneity of schizophrenia, SPDSE may be a disease subtype of schizophrenia with the aforementioned symptomatic features; and the EEM parameters may detect this subtype. Therefore, EEM may be one of the contributors to the simplification of the heterogeneity of schizophrenia. Consequently, we may apply EEM to other scientific studies as an endophenotype for schizophrenia.

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# Changing the mind? Not really—activity and connectivity in the caudate correlates with changes of choice

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**Changes in preference are inherently subjective and internal psychological events. We have identified brain events that presage ultimate (rather than intervening) choices, and signal the finality of a choice. At the first exposure to a pair of faces, caudate activity reflected the face of final choice, even if an initial choice was different. Furthermore, the orbitofrontal cortex and hippocampus exhibited correlations only when the subject had made a choice that would not change.**

**Keywords:** caudate; changing mind; face preference; fMRI; gaze manipulation

## INTRODUCTION

Why do we sometimes change our mind?

In the last several decades, psychologists have learned a lot about the neural basis of decision making (Kable *et al.*, 2009; Pennartz *et al.*, 2009). However, the distinction between sustained and transient decisions and the possibility that the decision may be overturned later have been largely neglected. We know from daily experiences that when we have to make a choice/decision, we sometimes reach a firm decision, but at other times we change our mind. However, so far we have not been able to identify the neural basis or the temporal dynamics of decision change or 'changing the mind'. Changing mind regarding a preference is especially interesting, because of its exclusively subjective and internal nature. Recent studies have identified the so-called 'binary attractor model' as being behind the behavioral change process involving single decisions, but they have not revealed much about the internal process that leads to a change in an already-made decision and its neural correlates (Resulaj *et al.*, 2009; Krajbich *et al.*, 2010; Albantakis and Deco, 2011). It has been difficult in the laboratory to obtain meaningful behavioral and neural data about the mechanisms involved in 'changing the mind' phenomenon, for a variety of methodological and technical reasons, including the difficulty to generate frequent 'real' responses associated with a change of mind and to find a paradigm to systematically manipulate preference decisions. In this study, we aimed to reveal the temporal dynamics of the changing mind in a serial time task, especially in terms of its neural basis. To the best of our knowledge, this was the first study that employed this approach; there were little evidences that could reveal the neural basis or the temporal dynamics of the decision change; that is the changing mind. Especially, the changing mind of preference decisions is interesting due to its exclusively subjective, internal nature.

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According to previous studies, attractive faces activate reward-related neural circuits. In particular, the striatum [putamen and nucleus accumbens (NAcc)]; the orbitofrontal cortex (OFC) is involved in face attractiveness judgment (Kim *et al.*, 2007; Tsukiura and Cabeza, 2011; Mende *et al.*, 2012). A recent study showed that there is a significant correlation between face attractiveness and hippocampal activation. This too suggests that the OFC and the hippocampus may be important for the evaluation of face attractiveness (Tsukiura and Cabeza, 2011). Furthermore, these results indicate that the evaluation of facial attractiveness is not only based on reward-related, but also on memory-related neural circuits.

The rationale behind the current study is as follows: since the preference decision and, in particular, its change are subjective and internal in nature, it is hard to explain them in terms of stimulus-driven, deterministic mechanisms. Therefore, we sought an alternative explanation as well as some physiological evidence to substantiate our rationale. We focused on the following three hypotheses regarding the neural correlates of the 'changing the mind' phenomenon.

(1) Changing the mind is 'real', in the sense that the entire brain consistently reverses the dominance in its activity, starting from the most upstream process in the neural information-processing cascade, possibly because of sensory or attentive modulations.
(2) Changing the mind is 'not real'. Although reversal takes place at the behavioral (and thus the downstream decoding) levels, such as the motor cortices, possibly due to some noise, the upstream subcortical areas do not change the dominance or the relative strength of their neural activity.
(3) There is always competition between two potential choices in neural circuits or brain activities. Alternative neural circuits are competing and suppressing each other, until one reaches the threshold to generate a choice action. The 'changing the mind' phenomenon reflects fluctuations in such a neural competition (cf. 'Competition hypothesis', Reynolds and Desimone, 1999; Resulaj *et al.*, 2009).

Currently available data are consistent with Hypothesis 2 and, at least partly, with Hypothesis 3 as explained below. For example, Kim *et al.* (2007) have identified different neural components of the preference decision-making process in the time domain that indicate a signal transfer from the NAcc in the ventral striatum to the OFC

(Kim *et al.*, 2007). To test these hypotheses, we analyzed the temporal dynamics of the neural processes involved in face preference decision-making. To obtain frequent occurrences of mind changing in a systematically manipulated way, we employed the gaze manipulation paradigm (Shimojo *et al.*, 2003).

Unlike previous related studies (e.g. Tsukiura and Cabeza, 2011), which employed a task of absolute attractiveness evaluation of a single face, participants in the current study performed a two-alternative forced-choice task twice. We examined differences and fluctuations in neural activity between the choice-changed cases and choice-not-changed cases. The results showed that, if the caudate showed a higher activation to a face at first sight, the participant chose that face at the time of the second decision. This is true regardless of whether the face with the higher caudate activation happened to be the first choice or not. Moreover, the OFC and the hippocampus exhibited a functional correlation at the first decision period. In contrast, in the choice-not-changed cases these two regions showed the same correlation during the second decision. The preference choice did not change in subsequent decisions when the following two conditions were met: (i) the caudate exhibited a high activity at first sight and (ii) the OFC and the hippocampus showed a high functional correlation during the first preference decision. However, if one of these two conditions was not met during the first decision, the subsequent preference decision tended to be different. In principle, we may be able to determine the likelihood of changing mind by examining the activation of the caudate at the time of the first sight, because the caudate appears to 'know' if one changes one's mind.

## MATERIALS AND METHODS

### Participants

Thirty-six healthy volunteers gave written informed consent for this study, approved by the ethics committee of Tamagawa University. Participants were divided into three groups: Main Manip. group [Face Preference group with effective Gaze Manipulation; eight female, four male, age = 19.2 ± 0.38 (mean ± standard error of mean, SEM)], No Gaze Shift group (Face Preference group with ineffective Gaze Manipulation; six female, six male, age = 20.0 ± 0.26), and Roundness group (Face Roundness group with effective Gaze Manipulation; six female, six male, age = 19.9 ± 0.33). The No Gaze Shift and Roundness groups were used as the control groups to examine the effects of gaze manipulation.

### Stimuli

One-hundred and sixty different faces (80 female, 80 male) were generated with a computer program (FaceGen; Singular Inversions). All images were presented on a 19-inch screen at 1024 × 768 pixel resolution. The viewing distance was always 57 cm. Eye movements were tracked with an eye tracking system (Arrington Research).

### Prerating of faces

Before scanning, the Main Manip. and the No Gaze Shift groups were first asked to rate the facial attractiveness of the 80 female and 80 male faces on a scale from 1 to 7; the Roundness group rated the facial roundness of each face in the same way. After obtaining the ratings, faces were paired according to each participant's rating so that faces with close ratings were paired.

### Instructions

Participants in the Main Manip. and No Gaze Shift groups were asked 'Who would you like to approach and talk to?' and participants in Roundness group were asked 'Which face is rounder than the other?'.

### Task design and gaze manipulation

All participants underwent two functional magnetic resonance imaging (fMRI) scans, each consisting of 40 trials. A trial consisted of two-alternative forced-choice sessions (initial and final choice phases) and a gaze manipulation session (Figure 1, Supplementary Figures S1A and S1B). After the initial choice phase in each trial, participants performed the gaze manipulation and then the final choice phase. To randomize the task, the manipulation and the final choice phase were skipped in ~40% of all trials. In the choice phases, two faces appeared sequentially on the screen, and the participants were asked to choose the face according to the instructions by pressing a button within five stimulus presentation cycles. The cycle in which the participants pressed the button was termed the 'response cycle', and the immediately preceding cycle was termed the 'opening cycle'. The duration times of the fixation, the faces, and 'Which?' were 1500–3000, 50 and 1000 ms, respectively. In the gaze manipulation session, the Main Manip. and Roundness groups were exposed to the effective gaze manipulation and the No Gaze Shift group to the ineffective gaze manipulation. In the effective gaze manipulation, the two faces appearing in the initial choice phase were displayed six times each on the right or left side of the screen sequentially in random order, and the presentation time of each face was determined by the participant's choice in the initial choice phase. The presentation time of the chosen face in the initial choice session was 300 ms, and that of the unchosen face was 900 ms. In contrast, in the ineffective manipulation, the two faces were displayed six times each on the center of the screen sequentially in alternate order, and the presentation time of the two faces was 600 ms.

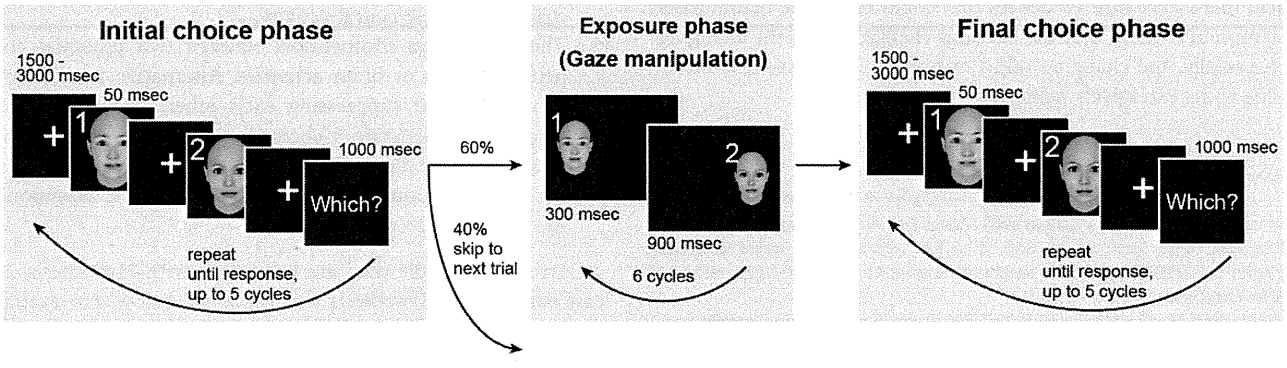


**Fig. 1** Iterated choice task design. A trial, using the same face pair throughout, consisted of an initial choice phase, a manipulated exposure phase, and a final choice phase. To randomize the task, 40% of trials ended after the initial choice. In choice phases, the two faces were presented in sequence, followed by an option to respond. The cycle was repeated, up to five times, until the subject indicated which person they would rather 'approach and talk to'. In the exposure phase, durations were biased toward the initially unchosen face to subconsciously bias subject preferences.

### Changing ratio

After the scans, we counted the number of the changing choices between the first choice session and second choice session, and calculated the changing ratio of the choice in each subject.

### Imaging procedures

Functional imaging was conducted on a 3-Tesla Siemens Trio Tim MRI scanner. For each participant, we acquired whole-brain T1-weighted anatomical scans and gradient echo T2 weighted echo planar images (EPI) with BOLD contrast (TR = 2000 ms; TE = 25 ms; slice gap, 0.6 mm; FOV, 192 mm; slice thickness, 3.0 mm; 34 oblique axial slices). We used a tilted acquisition sequence at 30° to the AC–PC line to recover signal loss in the medial orbitofrontal cortex (mOFC; Deichmann *et al.*, 2003). The first 5 volumes of images were discarded to allow for equilibration effects.

### Imaging data analysis

Image data were analyzed by using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). To correct for participants' motion, the images were realigned to the mean volume image and spatially normalized to a bias-corrected T1 image, and spatial smoothing was applied by using a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm.

Trials were separated into Firm Choice and Changed Choice trials on the basis of whether the initial and final choices matched or differed. We sorted the trials by the number of cycles required to make decisions and selected only the trials with two cycles to examine the temporal fluctuation of the neural activities and to compare the data with a previous report (Kim *et al.*, 2007). All MRI data in this article were limited to the Main Manip. group's data because the number of the Changed Choice trials in the other two groups were very small; thus, we could not detect any statistical differences in neural activity among the two groups. Each face presentation was treated as an event and categorized into chosen and unchosen faces as well as whether it was part of a Firm or Changed Choice trial. To avoid confusion, we refer to the faces on the basis of their status having been chosen or unchosen in the *final* choice phase.

Linear contrasts of regression coefficients (parameter estimates) were computed at the individual participant level in contrast to the final choice or the other face. The results from each participant were taken to a random effects level by including contrast images from each single participant into a paired *t* test. A statistical threshold at $P < 0.001$ or $< 0.005$ (uncorrected) was used.

### Region of interest extraction

We used the MarsBar tool for SPM (http://marsbar.sourceforge.net/) to extract activations from the spherical regions of interest (ROIs) centered on the peak coordinates for the significant caudate, hippocampus and OFC contrasts (arrows in Figures 3 and 4).

### Correlation analysis

In phases, where significant activity was found in the hippocampus and OFC, we used SPSS (IBM) software to run Pearson correlation analysis between contrast levels in the ROIs of the OFC and hippocampus.

### Statistical analysis

All statistical analyses were performed with SPSS software.

## RESULTS

### Behavioral results

One procedural complication posed by compressed laboratory experiments such as this one is the typical paucity of reported changes due to consistency bias and rote behavior patterns. Thus, during the middle exposure phase, we employed a gaze manipulation paradigm, which has been shown to subliminally bias subject preferences (Shimojo *et al.*, 2003). Control experiments with unmanipulated exposures and a 'roundness' choice task verified that this manipulation was successful in leading subjects to change their minds; however, only in the preference task ($P < 0.001$, Supplementary Figure S1C).

### The temporal dynamics of the changing mind

We analyzed fMRI activity in response to face presentations by performing comparisons for the face of *final* choice *vs* the other face. These comparisons were performed for data from the first stimulus presentation cycle (opening cycle) and the last cycle prior to choice response (response cycle) separately (Figures 2, 3, 4, Supplementary Figures S2 and S3, and the main effects were shown in Supplementary Tables S1–S4). We divided the trials into Firm Choice trials, where subjects made the same choice in both phases, and Changed Choice trials, where the initial and final choices differed. As shown in Supplementary Figures S2 and S3, these final chosen *vs* unchosen face comparisons were statistically significant regardless of the size choice of ROIs.

### The effects of gaze manipulation on the face preference decision

To examine the effects of gaze manipulation on the preference decision, we compared the contrast between the initial choice and the final choice phase. The fMRI data revealed that there was an increase and inversion of the activity in the hippocampus and OFC only in the Changed Choice trials but not in the Firm Choice trials (Figure 2).

### The temporal dynamics of caudate activity during changing of mind

The caudate showed a significant contrast toward the face of the final choice in the opening cycles of both choice phases, and this was true for both Firm and Changed Choice trials (Figures 3A and 4A). The caudate activity exhibited a dynamic spatial pattern as the trial progressed. Significant activity began in the middle caudate and then moved to the anterior caudate (Figures 3A, D, 4A, B, D, and Supplementary Figure S4). In the Firm Choice trials, this pattern was more distinct with the middle caudate being significant only at the opening of the initial choice phase and the anterior caudate being significant only at the opening of the final choice phase. The Changed Choice trials showed a more sustained version of the same pattern (Figure 4B and D). The middle caudate extended its significant activity throughout the initial choice phase and into the opening of the final choice phase. The pattern of the anterior caudate began to increase in the initial choice phase and became significant at the opening of the final choice phase (Figures 3D and 4D).

### The functional correlation of the hippocampus and the OFC

The hippocampus and the OFC (Figures 3B, C, 4C, E and F) also showed significant contrast at selected phases and during the 'Which' response, which is the time to decide which face is preferable to the other and indicate it by pressing a button. We calculated the correlations between these regions during each choice phase. We found significant activity and correlations in phases where subjects made a firm or final choice, but not in phases where their choice was tentative

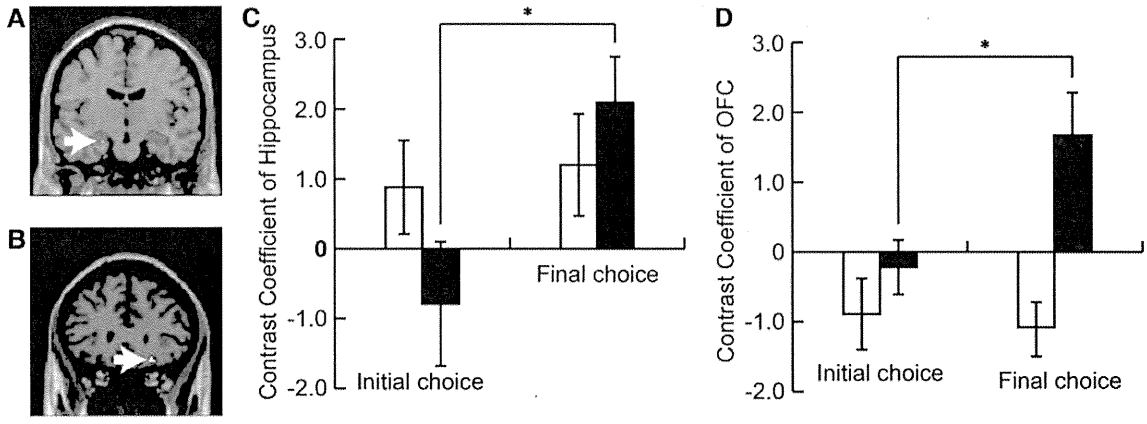


**Fig. 2** Gaze manipulation increased the activation of the hippocampus and the OFC. The contrast between the response cycles of the initial and final choice phase showed activations in the left hippocampus (**A**, −22, −12, −20) and the right OFC (**B**, 24, 30, −16). ROI analysis showed that these regions were activated only in the Changed Choice trials (**C**, **D**). These two regions were considered to play an important role in face attractiveness judgment. White arrows indicate the peak voxels in the hippocampus (**A**) and the OFC (**B**). White bars are Firm Choice, and black bars are Changed Choice trials. To define the activated regions, a statistical threshold at $P < 0.005$ (uncorrected) was used. Each peak voxel was used as the center of 4-mm radius spherical ROI. Error bars mean SEM; $^{*}P < 0.05$. All MRI data are from the Main Manip. group.

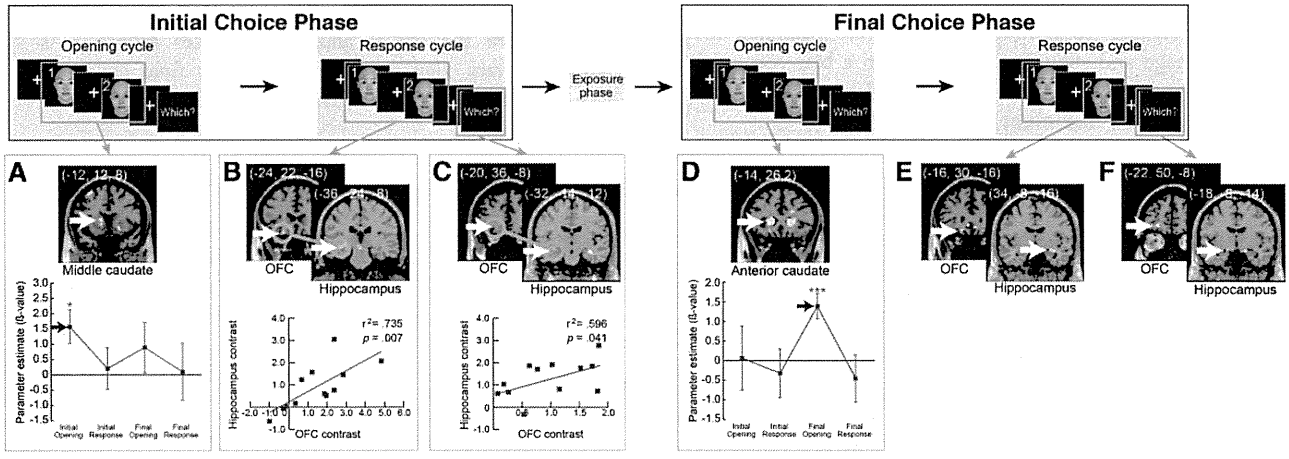


**Fig. 3** Significant activity contrasts and correlations at successive cycles of the Firm Choice trials. Initial choice phase and Final choice phase trials were analyzed separately. White arrows indicate the peak voxels in the caudate, the hippocampus, and the OFC. (**A**, **D**) The bottom graphs show the time course of caudate activity. (**B**, **C**) Blue circles indicate a significant correlation of contrast levels between the hippocampus and OFC, and subject-by-subject plot of contrast levels in hippocampal *vs* OFC ROIs, indicating significant correlations. To define the activated regions, a statistical threshold at $P < 0.005$ (uncorrected) was used. $^{***}P < 0.001$, $^{**}P < 0.005$, $^{*}P < 0.01$.

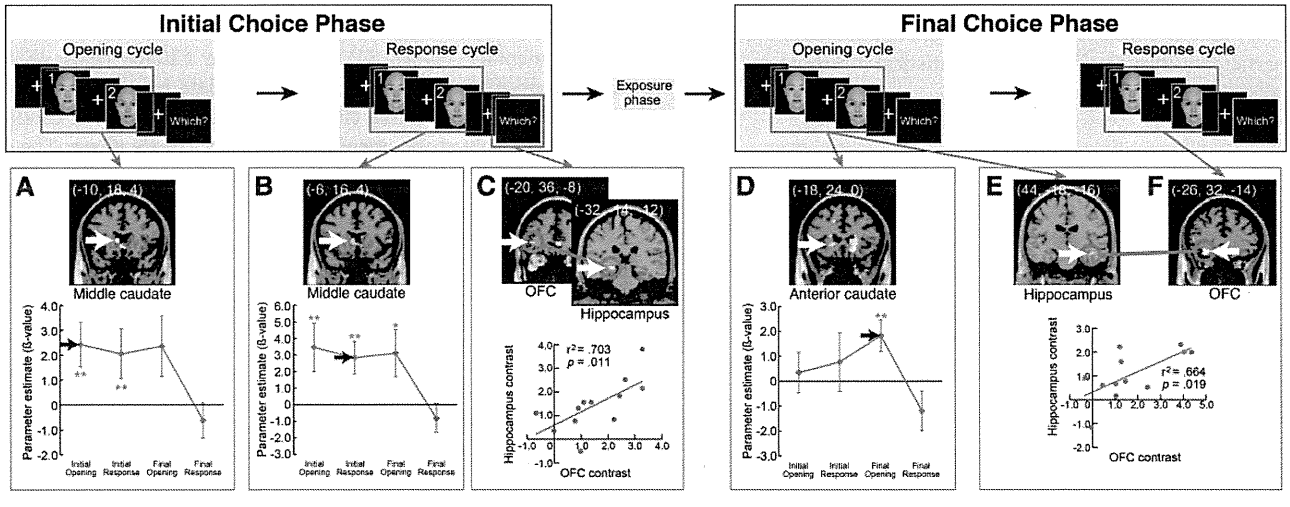


**Fig. 4** Significant activity contrasts and correlations at successive cycles of the Changed Choice trails. Initial choice phase and Final choice phase trials were analyzed separately. White arrows indicate the peak voxels in the caudate, the hippocampus and the OFC. (**A**, **D**) The bottom graphs show the time course of caudate activity. (**C**, **E**, **F**) Red circles indicate a significant correlation of contrast levels between the hippocampus and OFC, and subject-by-subject plot of contrast levels in hippocampal *vs* OFC ROIs. To define the activated regions, a statistical threshold at $P < 0.005$ (uncorrected) was used. $^{***}P < 0.001$, $^{**}P < 0.005$, $^{*}P < 0.01$.

and was going to change. In the Firm Choice trials, significant contrast and correlation was present in the initial choice phase (Figure 3B and C, blue circles and bottom scatter-plot). In the final choice phase, where subjects stuck to their earlier choice, there was also a significant contrast in both areas (Figure 3E and F), but they lacked the correlation between the hippocampus and the OFC. In Changed Choice trials, there was no significant contrast in the response cycle in the initial choice phase in which the subjects responded with a choice that was later reversed. However, there was a correlation between the hippocampus and the OFC in the 'Which' response timing (Figure 4C). Significant contrast and correlation was present in the final choice phase (Figure 4E and F, red circles and bottom scatter-plot). Finally, we also found a significant contrast in the ACC and the DLPFC; however, only in the Changed Choice trials (Supplementary Figure S5).

## DISCUSSION

We identified the neural basis underlying the changing of mind, and the dynamic process appears be as follows: At first sight (initial opening cycle), (i) the caudate is activated in response to 1 face (we call it 'Caudate-dominant face') over the other ('Caudate-nondominant face'). In other words, caudate activity reflects the final choice even at the very beginning of the trial, even when the subject is about to make an initial choice favoring the opposite face. This might lead to (ii) a functional correlation between the hippocampus and the OFC, which provides the conditions for the choice. The Caudate-dominant face is typically selected for the initial choice; however, occasionally the Caudate-nondominant face is selected possibly due to noise or fluctuations in competition. Indeed, only in the Choice Changed trials, the ACC and the DLPFC, which are well-known regions to correlate with a decision conflict and resolution, (MacDonald *et al.*, 2000; Milham *et al.*, 2001; Pochon *et al.*, 2008) showed high activation (Supplementary Figure S5). While we admit that this is a *post hoc* interpretation of the activity, the known functions of these areas and the specificity to the Choice Changed trials seem to be highly consistent.

It is likely that when (i) and (ii) above are satisfied, the choice is maintained in the final judgment. When these conditions are not met, a change of mind is likely to occur. Interestingly, even in such cases, there is an increase in the activity of both the hippocampus and the OFC as well as in the functional correlation in response to a newly chosen face. However, there were some laterality differences in the connected regions (Figures 3B, C, 4C, E and F) and the increase in activity (Figure 2). This is logical if we consider that the second choice is firmer than the first one in the Choice Changed trials. Either way, our findings add a significant constraint on the manipulation effect—it reverses the choice, only (or mostly) when the neural response to the finally chosen object is high in the memory-related brain circuits (such as the hippocampus–OFC network) from the beginning. Meanwhile, the transitions from the middle to the anterior caudate (Figures 3A, D, 4A, B and D) might reflect a progression in consolidation of a preference tendency into firm preferences. Along with the shift in caudate activity, the hippocampal and OFC activity might also possibly be involved in the consolidation of a preference tendency into a firm decision. Alternatively, the activity could reflect ancillary processes such as a memory process that was engaged because of the decision (Tsukiura and Cabeza, 2011).

More precisely, our findings provide a new insight into the temporal neural processing during face preference decisions, especially regarding the function of the caudate, OFC and hippocampus. The ventral striatum and the OFC are two major subcortical and cortical regions, respectively, which have been strongly implicated in reward-related processing (Knutson *et al.*, 2001; Cardinal *et al.*, 2002; O'Doherty *et al.*, 2001). In general, the ventral striatum is involved in encoding errors in predicting future rewards (i.e. the reward anticipation), whereas the OFC is involved in encoding stimulus-reward value and in representing expected future rewards (O'Doherty *et al.*, 2004). The present data indicate a distinct contribution of these two reward-related regions in terms of temporal dissociation and consolidation during face preference decision-making. As shown by the caudate activity at first sight (the opening cycle of the initial choice phase), the relative evaluation of two faces was made instantly without any delay. The information was then transferred from the caudate to the OFC and the hippocampus, which are anatomically connected (Barbas and Blatt, 1995; Carmichael and Price, 1995; Lavenex *et al.*, 2002). This functional connectivity between the OFC and hippocampus during face preference judgment reflects the positive signals generated by an attractive face (Tsukiura and Cabeza, 2011) and is possibly involved in the consolidation of a preference tendency into a firm decision. The current study demonstrates such a serial transfer of the preference signal from the subcortical level to the cortical level for the first time. At the same time, it also indicates that such a signal transfer often does not work; for example, in the Choice Changed cases. In a sense, the process of changing of mind is very simple; signal transfer is disrupted by some conflicting signals representing the activity of the ACC and the DLPFC, and the participant's choice is not consistent with a Caudate-dominant face. In such cases, the choice is changed rapidly.

Moreover, our data may be interpreted as, changing of mind does not really occur in the narrower sense. It can be argued that the future decision has already been made implicitly at first sight and never been changed (as indicated by the early caudate activity). It may be because of random noise or fluctuation in the downstream processes, or overridden by the cortical deliberation system and, therefore, the 'dominant' face was not chosen in the initial decision. In the final decision, the original evaluation is transferred from the caudate (implicit, subcortical level) to the hippocampus and OFC (explicit, cortical level) because of the gaze manipulation, and this transfer enables the so-called changing of the mind. This interpretation is different from a more integrated/consistent view of decision making, but rather reminiscent of the 'neural competition of choices' idea (Reynolds *et al.*, 1999; Resulaj *et al.*, 2009). The results may be applicable to various other cases of decision changes in the laboratory and in everyday life.

## SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

### Conflict of Interest

None declared.

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# How Sound Symbolism Is Processed in the Brain: A Study on Japanese Mimetic Words

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## Abstract

Sound symbolism is the systematic and non-arbitrary link between word and meaning. Although a number of behavioral studies demonstrate that both children and adults are universally sensitive to sound symbolism in mimetic words, the neural mechanisms underlying this phenomenon have not yet been extensively investigated. The present study used functional magnetic resonance imaging to investigate how Japanese mimetic words are processed in the brain. In Experiment 1, we compared processing for motion mimetic words with that for non-sound symbolic motion verbs and adverbs. Mimetic words uniquely activated the right posterior superior temporal sulcus (STS). In Experiment 2, we further examined the generalizability of the findings from Experiment 1 by testing another domain: shape mimetics. Our results show that the right posterior STS was active when subjects processed both motion and shape mimetic words, thus suggesting that this area may be the primary structure for processing sound symbolism. Increased activity in the right posterior STS may also reflect how sound symbolic words function as both linguistic and non-linguistic iconic symbols.

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**Competing Interests:** The authors have declared that no competing interests exist. In Figure 1, the authors present pictures of people walking. This person is the first author of this manuscript.

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## Introduction

Traditional linguistics assumes that language is independent from perceptual, motor, or affective experience and that pairings between a word's sound and its meaning are arbitrary [1]. The notion of sound symbolism, however, challenges this well-accepted belief by suggesting natural and systematic relationships between word sound and meaning [2]. People across the world intuitively associate the nonsense word "baluma" to a round shape and "takete" to a spiky shape (i.e., bouba/kiki effect) [3–4]. Since then, a large body of linguistic and psychological research has investigated sound symbolism (e.g., [5]). Sound symbolic words are found in many languages including English. For example, *bump* and *thump* have sounds similar to their meanings–an event with an abrupt end [6]. Furthermore, a number of languages, including Japanese, have a large grammatically defined word class in which sound symbolism is apparent. These sound symbolic words, which are called mimetics, idiophones, or expressives, are abundant in African [7] and East Asian languages [8–14]. Adults [15–16], as well as infants and toddlers [17–22], are sensitive to sound symbolism in mimetic words, regardless of the language they speak. For example, the sound symbolism of Japanese mimetic words promotes verb learning in both Japanese- and English-reared children [18–20]. The existence of sound symbolism across languages has led some researchers to claim that this phenomenon can provide insights into the ontogenesis and phylogenesis of language [4,18,23]. Despite its significance, the neural mechanisms of sound symbolism are yet to be sufficiently investigated.

Ramachandran and Hubbard [4] hypothesized that sound symbolism shares the neural mechanisms underlying synesthesia. They further argue that multi-sensory integration at the temporal–parietal–occipital (TPO) junction, or more specifically the angular gyrus, is the critical region for sensing sound symbolism. In addition, they noted anecdotally that individuals with damage to the angular gyrus did not show the bouba/kiki effect. Nevertheless, these ideas are largely speculative and have never been investigated empirically.

We agree with this previous hypothesis that perceiving sound symbolism requires a unique integrative process. We hypothesize, however, that the posterior part of the superior temporal sulcus (STS) is a key area in this processing. The STS represents 2 routes for conceptual access: the left STS processes linguistic sounds, whereas the right STS processes environmental sounds [24]. The universal understanding of mimetic words suggests that these words possess some features of non-linguistic environmental sounds that do not require language system for understanding. We argue that neural processing of sound symbolic words

integrates the two conceptual processes involving the bilateral STS.

A previous functional magnetic resonance imaging (fMRI) study found that auditory presentation of Japanese mimetic words for animal sounds (e.g., *ka-ka*, onomatopoeia for crow croaks) more strongly activated the right STS than the names of the animals (e.g., *karasu*, "crow" in English) [25]. Similarly, Japanese mimetic words for animal sounds more strongly activated the STS bilaterally than the actual animal sounds (e.g., sound of a crow croaking). That study concluded that onomatopoeic words activate both the left and right STS because they have acoustic properties similar to real animal sounds. The acoustic similarity between mimetic words and the actual sound, however, cannot fully explain the phenomenon of sound symbolism, because sound symbolic words are not limited to mere mimicry of environmental sounds.

For example, Japanese mimetic words are roughly classified into 3 categories–phonomimes, phenomimes, and psychomimes [26]. Phonomimes, or *giongo*, are onomatopoeia that acoustically imitate actual sound (e.g., *wanwan* for dog barking). Phenomimes, or *gitaigo*, represent the characteristics of input from non-auditory senses (e.g., *yotayota* for walking clumsily). Psychomimes, or *gijogo*, represent psychological states (e.g., *wakuwaku* for the feeling of excitement). Several studies demonstrated that Japanese as well as non-Japanese speakers can discern sound-meaning correspondences in the latter two types of mimetics [18–20,27,28]. Sound symbolism in English, such as *squeeze*, *squirt*, *squint*, *bump*, *thump*, and *plump* [6], are found beyond the non-auditory domain as well. Thus, in order to fully understand the neural processing of sound symbolism, we must investigate sound symbolism in the non-auditory domain.

We hypothesize that right STS participation can differentiate sound symbolic words from non-sound symbolic words. Therefore, all types of mimetic words, including phenomimes and psychomimes, should activate the right STS. To determine whether the right STS is the primary structure for sound symbolism processing, we investigated whether this region responds to non-onomatopoeic mimetic words. For this purpose, we tested mimetics in two domains, motion and shape, and all words were presented visually rather than auditorily. Experiment 1 contrasted Japanese mimetic words with non-sound symbolic conventional verbs and adverbs, all of which express aspects of human motion. Experiment 2 compared the neural processing of mimetic words for human motion as well as for shape to ensure that the right STS activation is not limited to the domain of motion. Interpretation of the STS activation in Experiment 1 requires caution because the STS shows activation during the processing of animated figures [29,30] and point-light biological motion [31]. If the right STS is the key structure for sound symbolism processing, we should see the activation of this area both for motion mimetic words and for shape mimetic words. Experiment 2 tested mimetic words only, as differences in brain activation across word classes (mimetic words, verbs, and adverbs) were demonstrated in Experiment 1, and as with inclusion of multiple word classes would substantially increase the length of each scanning session.

## Materials and Methods

### Experiment 1

**Participants.** Sixteen native Japanese speakers aged 22–25 years (7 women, 9 men; mean age = 23.7 years) participated in this study. All participants were right-handed, had normal or corrected-to-normal vision, and had no history of neurological or psychiatric symptoms. Data from 5 participants were excluded due to artifact (e.g., head movements >3 mm) or inadequate task performance (e.g., failing to press buttons as instructed during scanning sessions); thus data were analyzed from the remaining 11 participants (4 women, 7 men; age range = 22–25 years; mean age = 23.4 years). The individual in this manuscript has given written informed consent to publish these case details. The study was approved by the ethics committee of Tamagawa University.

**Design and procedure.** Stimuli were 16 video clips of a human agent moving from left to right in different manners. Each video clip was 5-sec long, and was presented simultaneously with a sound symbolic mimetic word, a non-sound symbolic adverb, or a non-sound symbolic verb. All words were presented at the bottom of the video in *hiragana* (a type of Japanese orthographical coding in which each character represents a syllable). In half of the trials, the word and manner of motion semantically matched, whereas in the other half, the items were mismatched (e.g., the verb *aruiteiru* "to walk in the progressive aspect," was shown with a video clip of an agent skipping). Thus, for each word class (mimetic words, verbs, or adverbs), 8 motion-word pairs were matched and 8 pairs were mismatched. Participants were instructed to determine the degree of match between the word and the motion as the video clips were presented. After each video clip, a fixation point appeared on the screen for 3 sec, and participants indicated the degree of match between the word and the motion on a scale of 1 to 5 by pressing the appropriate button with a right-hand finger (Figure 1). As Experiment 1 used a 1.5 scanner, we used a block design to maximize sensitivity to the brain response: 4 blocks were presented for each word class (mimetic words, verbs, or adverbs), with each block consisting of 4 motion-word pairs from the same word class. The order of the blocks was rotated among participants. A fixation point was inserted for 10 sec at the end of each block.

**Stimuli and stimulus validation.** Three pretests examined 120 preselected words to ensure that the mimetic words, verbs, and adverbs were balanced in terms of imageability, familiarity, and age of acquisition (AOA). Twenty-eight participants who were native-Japanese speakers rated how imageable each word was on a scale of 1 to 7. Twenty-seven participants categorized word familiarity on a scale from 1 to 7. Twenty-two participants were asked to indicate the approximate age at which they learned words from the following 8 categories: infancy, preschool, first to third grade, fourth to sixth grade, junior high school, high school, university or college, or do not know the meaning. The pretest results indicated significant differences among the 3 word classes with respect to imageability (mimetic words: 5.28; verbs: 6.40; adverbs 5.62; $F(2,81) = 3.11$, $p<0.05$) and familiarity (mimetic words: 5.42; verbs: 6.51; adverbs: 6.08; $F(2,78) = 3.11$, $p<0.05$); although mimetic words and adverbs did not significantly differ in imageability ($t(27) = 1.200$, $p = 0.241$). The results of the AOA survey indicated that participants acquired mimetic words and verbs earlier than adverbs (mean rating scores were 1.52 for mimetics, 1.55 for verbs, and 2.93 for adverbs); however, no significant difference was found between AOA of the mimetic words and verbs (Freedman test, $p = 0.76$).

**Materials and imaging parameters.** Imaging was performed using a 1.5-T MRI scanner (SIEMENS MAGNETOM SONATA, Erlangen, Germany). A high-resolution (1×1×1 mm) T1-weighted anatomical reference image was acquired from each participant using a rapid acquisition gradient echo (MP-RAGE) sequence. Multi-slice gradient echo planar imaging (EPI) was used with a TE of 50 ms and a TR of 2000 ms. Slice-acquisition was ascending within the TR interval. The matrix acquired was 64×64 voxels with a field of view of 192 mm, resulting in an in-plane resolution of 3 mm. Slice thickness was 3 mm (20 slices, whole brain coverage).

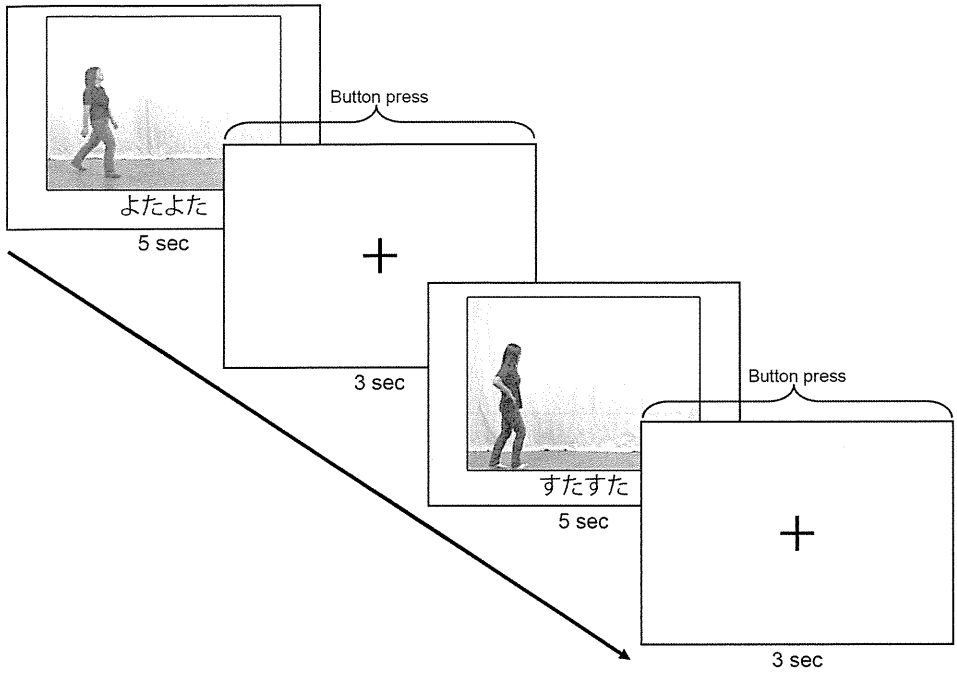


**Figure 1. Study paradigm for Experiment 1.** Experiment 1 used a blocked design. A 5-sec video clip presented a person moving from left to right and a matched/mismatched word that were followed by a 3-sec presentation of a fixation point. Participants were asked to press a button during the fixation point presentation to indicate the degree of match, on a scale of 1–5, between the motion and the mimetic words. This example shows two trials in the mimetic word block. The mimetic words depicted in this example: よたよた (*yotayota*) "walk clumsily" and すたすた (*sutasuta*) "walk very quickly".
doi:10.1371/journal.pone.0097905.g001

**fMRI data analyses.** fMRI data were analyzed using SPM8 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). The gradient-echo echo-planar images for each time series were realigned with reference to the first image acquired in each session to correct for head motion. The anatomical images were co-registered with the mean functional images and normalized to the Montreal Neurological Institute (MNI) brain template. Functional data were normalized using the same transformation parameters and smoothed in the spatial domain (isotropic Gaussian kernel of 8 mm full width half-maximum). Low-frequency drifts were removed using a high-pass filter [32], and a first order autoregressive model (AR1) [33] was applied for eliminating the temporal autocorrelation of the fMRI time series data.

The fMRI time series for each participant were analyzed using a block design approach with a general linear model. The images were sorted by trial type (matched and mismatched trials), and regions unique to mimetic processing were calculated by subtracting verbs and adverbs from mimetic words. The vectors indicating the onset and duration of each of the 3 word classes (mimetic words, verbs, and adverbs) were convolved with a hemodynamic response function. The results for the single subject analyses were then used for group analyses. Images representing the estimated cerebral effects from the [mimetic words – verbs – adverbs] for each subject were analyzed using a one-way ANOVA to determine the consistency of the effects across subjects. To ensure that the activation patterns of mismatched motion-word pairs were different, the same procedure was conducted for mismatched pairs.

## Experiment 2

**Participants.** Fifteen native Japanese speakers aged 17–26 years (8 women, 7 men; mean age: 20.93 years) participated in the fMRI study. All participants were recruited on the basis of the same criteria as in Experiment 1. Four participants were excluded from the analysis as not enough data were collected for these subjects (less than 10 trials in one condition). The final data set consisted of 5 women and 6 men (mean age: 21.13 years; range = 17–27 years).

**Stimuli.** One hundred and fourteen animation clips and their corresponding mimetic words were used in the main fMRI experiment. Each video clip depicted a simple line-drawing figure with hands and legs, and this "agent" either stayed still in the center of the screen or moved from left to right on a white background (Figure 2). The still and moving images were used for the shape and motion trials, respectively.

Twenty-four mimetic words referring to human motion and 35 mimetic words referring to shape were selected from a dictionary of Japanese mimetic words (*Giongo • Gitaigo 4500 Nihongo Onomatope Jiten*) [34]. Two separate rating tests, a web-rating test and a behavioral rating test, were conducted prior to the fMRI scanning to assure that the set of experimental stimuli contained both matched motion/shape-word pairs and mismatched motion/shape-word pairs. All participants who took part in the rating tests were native Japanese speakers who did not participate in Experiments 1 or 2.

In the web-rating test, 108 participants rated the degree of match between mimetic words and shapes/manners of motion on a scale of 1 to 5. 57 participants rated the degree of match between mimetic words and manners of motion, whereas 51 participants rated the degree of match between mimetic words and shapes. Each participant was presented with 105 pairs of words and their referents. From this analysis, 50 manners of motion and 48 shape figures were selected.

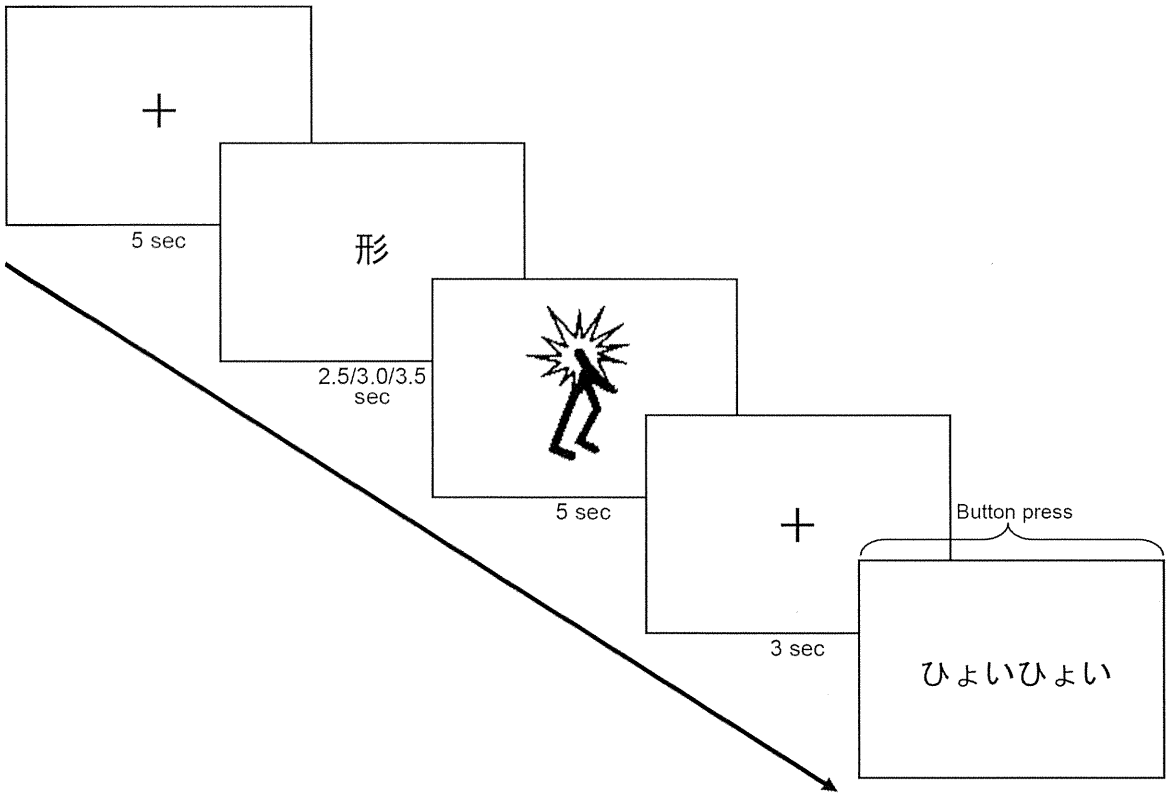


**Figure 2. Study paradigm for Experiment 2.** Experiment 2 used an event-related design. Stimuli were presented in the following order: 5-sec fixation point, 1-word instruction (presented either for 2.5, 3.0, or 3.5 sec) indicating the trial type ( 形 "shape" or 動き "motion"), 5-sec video clip, 3-sec fixation point, and a mimetic word. Video clips depicted an agent who stayed still in the shape trials and moved from left to right in the motion trials. During the presentation of a mimetic word, participants pressed a button to indicate the degree of match between the referent and the mimetic word. The mimetic word depicted in this example is ひょいひょい (*hyoihyoi*) which means "jumping effortlessly" in this context.
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After the web rating test, the remaining manners of motion and shapes were combined to create animation clips of an agent that was either motionless or that moved across the display, as described above.

In the behavioral rating test, 29 participants rated each stimuli pair (motion/shape and word) in the same manner as the scanning experiment. Thirteen shape/motion-word pairs that were judged as neither matched nor mismatched were excluded at this point. The final set of stimuli consisted of highly matched (mean rating score: 4.16 and 4.30 for the motion trials and shape trials respectively) and mismatched pairs (mean rating score: 1.34 and 1.29 for the motion trials and shape trials respectively). A total of 114 video clips (57 for each modality) were used in the fMRI experiment.

**Design and procedure.** Each shape or manner of motion appeared 1–8 times, and each shape-motion combination was different. Thus, participants saw each video clip once. A fixation point was presented for 5 sec, which was followed by a one-word instruction (either "motion" or "shape") that directed participants to attend to either the motion or shape of the agent in the animation clip. The duration of the instruction was jittered and was 2.5, 3, or 3.5 sec; the duration for all video clips was 5 sec. After each video clip, a sound symbolic mimetic word was visually presented. In some trials, the mimetic word and indicated visual property (motion or shape) were semantically matched, but these were mismatched in other trials (e.g., a hopping motion followed by the word *yotayota* "to walk clumsily"). Participants judged the degree of match between the manner of motion in motion trials and the shape of the agent and mimetic word in shape trials. Participants pressed 1 of 5 buttons while the mimetic word was on screen. 11 Stimuli sequences were presented in pseudo-random order to control the order effects, and all words were shown in *hiragana*.

**Imaging parameters and analysis.** Scanning was performed with a 3.0-T MRI scanner (Siemens MAGNETOM Torio-Tim, Erlangen, Germany). A high-resolution (1×1×1 mm) T1-weighted anatomical reference image was acquired from each participant using a rapid acquisition gradient echo (MP-RAGE) sequence. Multi-slice gradient echo planar imaging (EPI) was used with a TE of 25 ms and a TR of 2500 ms. Slice-acquisition was ascending within the TR interval. The matrix acquired was 64×64 voxels with a field of view of 192 mm, resulting in an in-plane resolution of 3 mm. Slice thickness was 3 mm (42 slices, whole brain coverage). The acquisition window was tilted at an angle of 30° relative to the AC-PC line in order to minimize susceptibility artifacts in the orbitofrontal cortex. The fMRI data were analyzed using SPM8 software and preprocessed using the steps described for Experiment 1.

We classified the trials as matched trials with high rating scores (4 or 5) or mismatched trials with low rating scores (1 or 2). Statistical analysis of the behavioral data was performed using 2 factors: Modality (motion/shape) and Degree of Match (matched/mismatched). Thus, the trials were divided into 4 cell means: Shape-High (shape trials with a high rating score), Shape-Low (shape trials with a low rating score), Motion-High (motion trials with a high rating score), and Motion-Low (motion trials with a low rating score). For fMRI analysis, we focused on highly