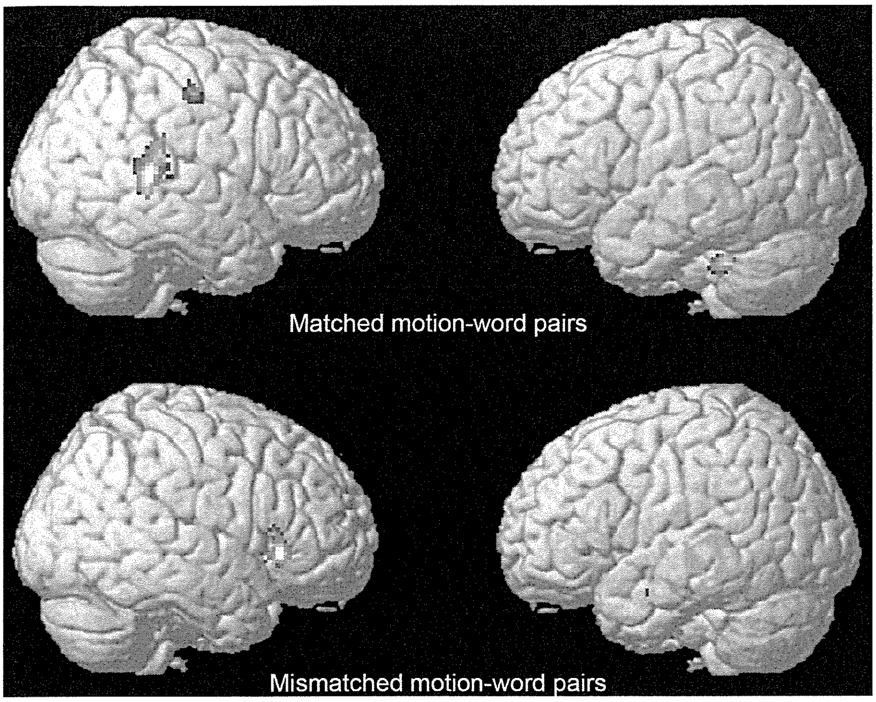


Figure 3. Results of Experiment 1. Regions that showed greater activation for mimetic words than for non-mimetic verbs and adverbs ($p < 0.05$, FWE corrected; see Materials and Methods).
doi:10.1371/journal.pone.0097905.g003

matched word-referent pairs, and thus highly matched trials (Shape-High and Motion-High) and mismatched trials (Shape-Low and Motion-Low) were analyzed separately. General Linear Model EPI time series were analyzed using the general linear model function implemented in SPM8. At the first level (i.e., within subjects), Shape-High, Shape-Low, Motion-High, and Motion-Low were modeled separately, creating 4 regressors. At the second level (i.e., across subjects), a one-sample *t*-test was performed on each regressor to examine the activation level.

Results

Experiment 1

Behavioral results. We examined whether the rated degree of match between the word and motion itself were comparable across the 3 word classes. For each word class, the degree of match was high for the highly matched pairs (mimetic words: 4.24; adverb: 4.30; verb: 4.09) and low for the mismatched pairs (mimetic words: 1.65; adverb: 1.64; verb: 1.10). According to a 3×2 (Word class: mimetic words/verb/adverb × matched/mismatched) ANOVA, rating scores were significantly different between the matched and mismatched pairs ($F(1,10) = 166.06$, $p < 0.01$). The main effect of the word class was also significant ($F(1,10) = 5.53$, $p < 0.05$). As indicated by the post-hoc test, the significant main effect for the word class was due to the difference between adverbs and verbs ($p = 0.05$, Bonferroni corrected), but the rating scores were similar between mimetic words and adverbs and between mimetic words and verbs ($p > 0.05$). Reaction times (RTs) were not analyzed in Experiment 1 as participants were instructed to delay their response until each video clip was over.

Table 1. Activation for mimetic words (Experiment 1).

Region of activation	Lat.	Coordinates			T-score	*k*
		x	*y*	*z*		
(Matched motion-word pairs)						
superior temporal sulcus	R	52	−36	14	6.53	398
post-central gyrus	R	40	−20	44	9.63	145
parahippocampal gyrus	L	−30	−10	−14	7.19	170
Cerebellum	L	−28	−38	−36	7.18	151
(Mismatched motion-word pairs)						
parahippocampal gyrus	L	−26	−18	−18	5.98	251
inferior frontal gyrus	R	42	22	8	5.56	288

Note: coordinates (mm) are in MNI space. L = left hemisphere; R = right hemisphere. $P < 0.001$ (uncorrected), $k > 140$, $P < 0.05$ (FWE corrected).
doi:10.1371/journal.pone.0097905.t001

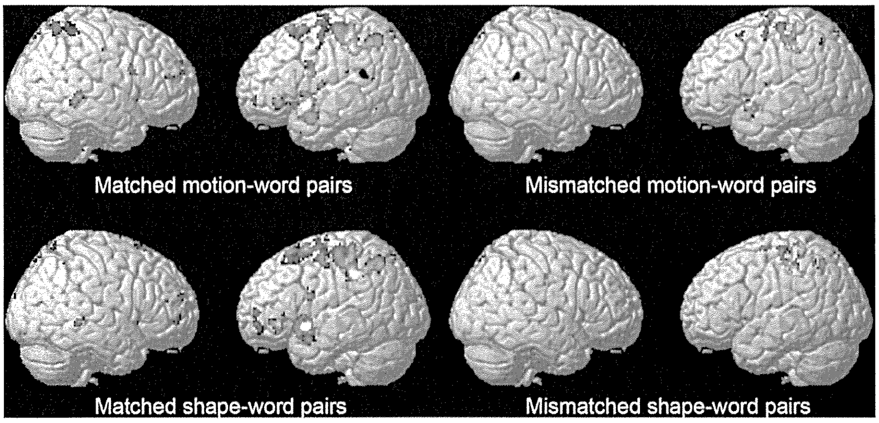


Figure 4. Results of Experiment 2. Several brain regions, including the right posterior STS, showed significant activation compared to baseline ($p<0.01$, FWE corrected). A strict threshold was used to ensure that the right pSTS was involved in the processing of both motion mimetic words and shape mimetic words. Brain activity observed during the motion and shape trials were not significantly different. However, the high-match trials elicited greater activation across the cortex than did low-match trials for either modality.
doi:10.1371/journal.pone.0097905.g004

Activation pattern for mimetic words. To identify the areas of activation for mimetic words, the images for verbs and adverbs were subtracted from the image of mimetic words (Figure 3; Table 1). As predicted, activation of the posterior part of the right STS was specific to mimetic words ($x=52$, $y=-36$, $z=14$; $T=6.53$; $p<0.05$, FWE corrected). The post-central gyrus, parahippocampal gyrus, and cerebellum were also activated by mimetic words. In contrast, we confirmed the right posterior STS was not significantly activated when motion and mimetic words were mismatched ($p>0.05$, FWE corrected). Mismatched mimetic motion-word pairs showed increased activation in the parahippocampal gyrus and inferior temporal gyrus.

Experiment 2

Behavioral results. We examined whether Modality (motion or shape) and Degree of Match (high or low) affected RTs. Using a two-way repeated measures ANOVA, we found that the RTs were significantly longer for the motion-word pairs than for the shape-word pairs ($F(1,10)=7.33, p=0.02$). However, there was no effect of Degree of Match ($F(1,10)=2.13$, $p=0.18$), or interaction between Modality and Degree of Match ($F(1,10)=0.88$, $p=0.37$).

General neural activation. Several brain regions, including the right posterior STS, showed significant activation compared to baseline (Table S1; Figure 4). Importantly, brain activation observed in the motion and shape trials did not significantly differ. However, the high-match trials elicited greater activation across the cortex than did low-match trials for either modality.

Region of interest analysis of the right posterior STS. The right posterior STS was activated in both motion and shape trials. To investigate whether the right posterior STS was activated for all conditions (matched motion, mismatched motion, matched shape, and mismatched shape), we performed a region of interest (ROI) analysis with a 3-mm ROI located at $x=62$, $y=-38$, $z=-2$ (Figure 5). This region was chosen based on the local maximum coordinates for the right posterior STS region. Although the right posterior STS was activated for all conditions compared to baseline, stronger activation was observed for matched motion/shape-word pairs. The main effect of Degree of Match was statistically significant (two-way ANOVA; $F(1,10)=8.06$, $p=0.02$); however, there was no significant effect of Modality ($F(1,10)=1.61$, $p=0.23$) or interaction between Modality and Degree of Match ($F(1,10)=0.84$, $p=0.38$). The RTs for the Degree of Match judgment were not different across matched and mismatched pairs. The behavioral results suggest that the task difficulty did not differ between the matched and mismatched pairs in which we found a difference in neural activation.

Discussion

In the present study, we investigated neural processing of sound symbolism using Japanese phenomimes. Despite accumulating evidence of universal sensitivity to sound symbolic word–meaning correspondences, the neural mechanism underlying this phenomenon has not been determined. Based on the idea of a functional dissociation of left and right STS [24], we hypothesized that the right posterior STS plays a critical role in sound symbolism processing. Experiment 1 tested this hypothesis by comparing Japanese mimetic words with verbs and adverbs for human motions. Supporting our hypothesis, mimetic words activated the right posterior STS even though all mimetic words were visually-presented phenomimes. This finding suggests that the function of

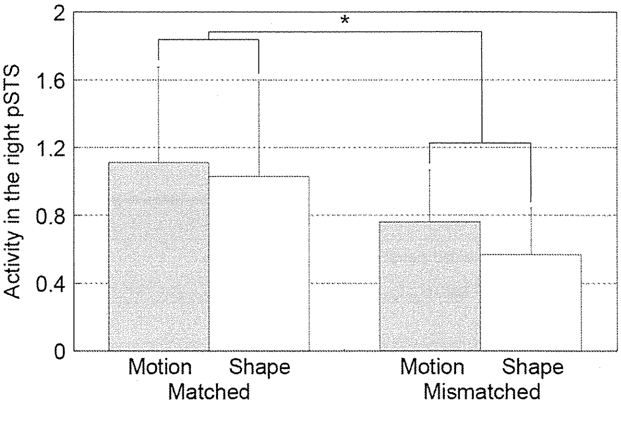


Figure 5. Mean beta values calculated in the ROI analysis for the right posterior STS (Experiment 2). Increased activation was observed for matched motion/shape-word pairs. A two-way ANOVA revealed the main effect of Degree of Match was statistically significant ($F(1,10)=8.06$, $p=0.02$). Error bars indicate ±1 standard deviation.
doi:10.1371/journal.pone.0097905.g005

the right posterior STS is not limited to the processing of onomatopoeia; rather, this area is likely responsible for the processing of mimetic words.

The results of Experiment 1, however, might indicate an alternative interpretation. STS is known to have multiple functions, one of which is processing biological motion. Right posterior STS activation may reflect an enhanced response to human motion caused by the paired presentation of biological motion and a mimetic word. Experiment 2 ruled out this alternative as the right posterior STS was activated not only for motion mimetic words, but also for mimetic words representing static shapes. For both motion and shape trials, the level of right posterior STS activation was higher when the mimetic word and referent were highly matched, further confirming that this region is sensitive to sound symbolism. We thus conclude that the posterior STS serves as a critical hub for processing Japanese mimetic words, and possibly sound symbolism in general.

Previous neuroimaging research on the neural processing of Japanese mimetic words focused only on the acoustic similarity between onomatopoeia (phonomimes) and environmental sounds [25] or the "embodied" explanation of sound symbolism [35]. The embodied explanation of sound symbolism suggests that a mimetic word activates a perceptual or sensorimotor area relevant to the word meaning. Similar claims have also been made for non-mimetic conventional words [36–43]. Thus, the embodied explanation does not explain why people sense the meaning in the sound of the word. In contrast, we suggest that sound symbolism processing requires a unique neural basis involving the posterior STS.

Although we must be cautious about drawing a reverse inference, the unique involvement of the right posterior STS in mimetic processing supports the idea that sound symbolic words are processed as both linguistic symbols and non-linguistic iconic symbols. We speculate that the posterior STS works as a hub of multimodal integration. Our view, therefore, corroborates that of Ramachandran and Hubbard [4] that linked the neural mechanisms of sound symbolism to synesthesia. Event-related potential (ERP) studies also suggest that sensory integration at the parietal-occipital regions is related to sound symbolism processing [42].

Importantly, however, Ramachandran and Hubbard [4] identified the (left) angular gyrus as the key region for high-level synesthesia. The angular gyrus and the STS are closely located but are two distinct structures. The disparity between these two claims may suggest that the distinct neural substrates are involved in sound symbolism and synesthesia. Alternatively, the nature of stimuli types may have affected the results, as sound symbolic words differ greatly in terms of modalities and level of iconicity. Our stimuli consisted of sound symbolic words that are part of the Japanese lexicon rather than nonsense sound symbolic words (e.g., "baluma" and "takete"). Conventional words and nonsense sound symbolic words may in part recruit different processing mechanisms.

Future research is required to investigate other types of sound symbolic words including psychomimes, non-mimetic words that carry sound symbolism (e.g., English sound emission verbs), and non-lexicalized sound symbolic words (e.g., "baluma" and "takete"). Comparative imaging research that includes other populations, such as young children, non-Japanese speakers, or synesthetic individuals, would also improve understanding of the origin of sound symbolism. Although research on the neural mechanisms underlying sound symbolism is in its early stages, such research has the potential to advance our understanding of language.

Sound symbolism is not a marginal phenomenon in language. Developmental research has demonstrated that Japanese mothers often say mimetic words to their children [44], and sound symbolism of Japanese mimetic words promotes verb learning [18–20]. Sound symbolism may also play a key role in revealing the origin of language. Some researchers suggest that when human language started with our primitive ancestors, it began through their oral mimicking of the observed world [4,17]. Thus, mimetic words may be similar to the words our ancestors used as a form of protolanguage. Sound symbolism, as a bridge between non-speech sound and conventional words, can provide new insights into the ontogenesis and phylogenesis of language.

Supporting Information

Table S1 Cortical activation for figure and motion (Experiment 2).
(XLSX)

Acknowledgments

We thank Mamiko Arata for her contribution in stimuli development and data collection and Guillaume Thierry for his insightful comments on an earlier version of the manuscript.

Author Contributions

Conceived and designed the experiments: JK TM MI JO HO. Performed the experiments: JK TM. Analyzed the data: JK TM. Contributed reagents/materials/analysis tools: JK TM. Wrote the paper: JK TM MI.

References

1. de Saussure F (1983) Course in general linguistics. La Salle: Open Court. 236 p.
2. Jakobson R, Waugh L (1979) The sound shape of language. Bloomington: Indiana University Press. 335p.
3. Köhler W (1929) Gestalt psychology. New York: Liveright Publishing Corporation. 384 p.
4. Ramachandran VS, Hubbard EM (2001) Synesthesia– a window into perception, thought, and language. J Cons Stud 8: 3–34.
5. Hinton L, Nichols J, Ohala J, editors (1994) Sound Symbolism. Cambridge: Cambridge University Press.
6. Firth JR (1957) The use and distribution of certain English sounds. In: Firth JR, editor. Papers in linguistics 1934–1951. London: Oxford University Press. PP. 34–46.
7. Childs GT (1994) African ideophones. In: Hinton L, Nichols J, Ohala JJ, editors. Sound symbolism. Cambridge: Cambridge University Press. PP. 178–206.
8. Diffloth G (1972) Notes on expressive meaning. In: Peranteau PM, Levi JN, Phares GC, editors. Papers from the eighth regional meeting of Chicago linguistic society. Chicago: Chicago Linguistic Society. PP. 440–447.
9. Lee J-S (1992) Phonology and sound symbolism in Korean ideophones [dissertation], Bloomington: Indiana University.
10. Nuckolls JB (1999) The case for sound symbolism. Annu Rev Anthropol 28: 225–252.
11. Mok WE (2001) Chinese sound symbolism: A phonological perspective [dissertation], Honolulu: University of Hawaii.
12. Watson RL (2001) A comparison of some Southeast Asian ideophones with some African ideophones. In: Voeltz FKE, Kilian-Hatz C, editors. Ideophones. Amsterdam: John Benjamins. PP. 385–405.
13. Enfield NJ (2005) Areal linguistics and mainland Southeast Asia. Annu Rev Anthropol 34: 181–206.
14. Bodomo A (2006) The structure of ideophones in African and Asian languages: the case of Dagaare and Cantonese. In: Mugane J, editor. Selected proceedings of the 35th annual conference on African linguistics. Somerville: Cascadilla Proceedings Project. PP. 203–213.
15. Nygaard LC, Cook AE, Namy LL (2009) Sound to meaning correspondences facilitate word learning. Cognition 112: 181–186.
16. Kovic V, Plunkett K, Westermann G (2010) The shape of words in the brain. Cognition 114: 19–28.
17. Maurer D, Pathman T, Mondloch CJ (2006) The shape of boubas: Sound-shape correspondences in toddlers and adults. Dev Sci 9: 316–322.

18. Imai M, Kita S, Nagumo M, Okada H (2008) Sound symbolism facilitates early verb learning. Cognition 109: 54–65.
19. Kita S, Kantartzis K, Imai M (2010) Children learn sound symbolic words better: Evolutionary vestige of sound symbolic protolanguage. In: Smith ADM, Schouwstra M, de Boer B, Smith K, editors. Proceedings of the 8th conference of Evolution of Language. World Scientific. London. PP. 206–213.
20. Kantartzi K, Imai M, Kita S (2011) Japanese sound symbolism facilitates word learning in English speaking children. Cogn Sci 35: 575–586.
21. Pena M, Mehler J, Nespor M (2011) The role of audiovisual processing in early conceptual development. Psychol Sci 22: 1419–1421.
22. Ozturk O, Krehm M, Vouloumanos A (2013) Sound symbolism in infancy: Evidence for sound-shape cross-modal corespondences in 4-month-olds. J Exp Child Psychol 114: 173–186.
23. Arbib MA (2005) From monkey-like action recognition to human language: An evolutionary framework for neurolinguistics. Behav Brain Sci 28: 105–167.
24. Thierry G, Giraud AL, Price C (2003) Hemispheric dissociation in access to the human semantic system. Neuron 38: 499–506.
25. Hashimoto T, Usui N, Taira M, Nose I, Haji T, et al. (2006) The neural mechanism associated with the processing of onomatopoetic sounds. Neuroimage 31: 1762–1770.
26. Akita K (2009) A grammar of sound-symbolic words in Japanese: Theoretical approaches to iconic and lexical properties of mimetics [dissertation], Kobe: Kobe University.
27. Iwasaki N, Vinson DP, Vigliocco G (2007) What do English speakers know about gera-gera and yota-yota? A cross-linguistic investigation of mimetic words for laughing and walking. Japanese-Language Education around the Globe 17: 53–78.
28. Iwasaki N, Vinson DP, Vigliocco G (2007) How does it hurt, "kiri-kiri" or "siku-siku"? Japanese mimetic words of pain perceived by Japanese speakers and English speakers. In: Minami M, editor. Applying theory and research to learning Japanese as a foreign language. Newcastle upon Tyne: Cambridge Scholars Publishing. PP. 2–19.
29. Pelphrey KA, Singerman JD, Allison T, McCarthy G (2003) Brain activation evoked by perception of gaze shifts: the influence of context. Neuropsychologia 41: 156–170.
30. Thompson JC, Clarke M, Stewart T, Puce A (2005) Configural processing of biological motion in human superior temporal sulcus. J Neurosci 25: 9059–9066.
31. Grossman E, Blake R (2002) Brain Areas Active during Visual Perception of Biological Motion. Neuron 35: 1157–1165.
32. Holmes AP, Josephs O, Büchel C, Friston KJ (1997) Statistical modeling of low-frequency confounds in fMRI. Proceeding of the 3rd international conference of the functional mapping of the human brain. Neuroimage 5: S480.
33. Friston KJ, Josephs O, Zarahn E, Holmes AP, Rouquette S, et al. (2000) To smooth or not to smooth? Bias and efficiency in fMRI time-series analysis. Neuroimage 12: 196–208.
34. Ono M, editor (2007) Giongo/Gitaigo 4500 nihongo onomatope jiten [Japanese Onomatopoeia Dictionary 4500 mimetics]. Tokyo: Shogakukan. 770 p.
35. Osaka N, Osaka M, Morishita M, Kondo H, Fukuyama H (2004) A word expressing affective pain activates the anterior cingulate cortex in the human brain: an fMRI study. Behav Brain Res 153: 123–7.
36. Martin A, Ungerleider LG, Haxby JV (2000) Category-specificity and the brain: The sensory-motor model of semantic representations of objects. In Gazzaniga MS, editor. The new cognitive neurosciences. 2nd ed. Cambridge: MIT Press. PP. 1023–1036.
37. Pulvermüller F, Harle M, Hummel F (2001) Walking or talking? Behavioral and neurophysiological correlates of action verb processing. Brain Lang 78(2): 143–168.
38. Hauk O, Johnsrude I, Pulvermüller F (2004) Somatotopic representation of action words in human motor and premotor cortex. Neuron 41: 301–307.
39. Hauk O, Pulvermüller F (2004) Neurophysiological distinction of action words in the fronto-central cortex. Hum Brain Mapp 21: 191–201.
40. Kable JW, Kan I, Wilson A, Thompson-Schill S, Chatterjee A (2005) Conceptual representations of action in lateral temporal cortex. J Cogn Neurosci 17: 1855–1870.
41. Tettamanti M, Buccino G, Saccuman MC, Gallese V, Danna M, et al. (2005) Listening to action related sentences activates fronto-parietal motor circuits. J Cogn Neurosci 17(2): 273–281.
42. Aziz-Zadeh L, Wilson SM, Rizzolatti G, Iacoboni M (2006) Congruent embodied representations for visually presented actions and linguistic phrases describing actions. Curr Biol 16(18): 1818–1823.
43. Kemmerer D, Tranel D (2008) Searching for the elusive neural substrates of body part terms: a neuropsychological study. Cogn Neuropsychol 25: 601–29.
44. Fernald A, Morikawa H (1993) Common themes and cultural variations in Japanese and American mothers' speech to infants. Phonetica 57: 242–254.

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 24 May 2013
doi: 10.3389/fnhum.2013.00221

Cerebral responses to vocal attractiveness and auditory hallucinations in schizophrenia: a functional MRI study

***Michihiko Koeda*[1,2]**, *Hidehiko Takahashi*[3], *Masato Matsuura*[4], *Kunihiko Asai*[5] *and Yoshiro Okubo*[2]**

[1] *Voice Neurocognition Laboratory, The Centre for Cognitive Neuroimaging, The Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK*
[2] *Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan*
[3] *Department of Psychiatry, Kyoto University, Kyoto, Japan*
[4] *Department of Biofunctional Informatics, Tokyo Medical and Dental University, Tokyo, Japan*
[5] *Asai Hospital, Chiba, Japan*

Edited by:
Paul Allen, King's College London, UK

Reviewed by:
Thomas P. White, King's College London, UK
Renaud Jardri, University Medical Centre of Lille, France

****Correspondence:***
Michihiko Koeda, Department of Neuropsychiatry, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
e-mail: mkoeda@nms.ac.jp

Impaired self-monitoring and abnormalities of cognitive bias have been implicated as cognitive mechanisms of hallucination; regions fundamental to these processes including inferior frontal gyrus (IFG) and superior temporal gyrus (STG) are abnormally activated in individuals that hallucinate. A recent study showed activation in IFG-STG to be modulated by auditory attractiveness, but no study has investigated whether these IFG-STG activations are impaired in schizophrenia. We aimed to clarify the cerebral function underlying the perception of auditory attractiveness in schizophrenia patients. Cerebral activation was examined in 18 schizophrenia patients and 18 controls when performing Favorability Judgment Task (FJT) and Gender Differentiation Task (GDT) for pairs of greetings using event-related functional MRI. A full-factorial analysis revealed that the main effect of task was associated with activation of left IFG and STG. The main effect of Group revealed less activation of left STG in schizophrenia compared with controls, whereas significantly greater activation in schizophrenia than in controls was revealed at the left middle frontal gyrus (MFG), right temporo-parietal junction (TPJ), right occipital lobe, and right amygdala ($p < 0.05$, FDR-corrected). A significant positive correlation was observed at the right TPJ and right MFG between cerebral activation under FJT minus GDT contrast and the score of hallucinatory behavior on the Positive and Negative Symptom Scale. Findings of hypo-activation in the left STG could designate brain dysfunction in accessing vocal attractiveness in schizophrenia, whereas hyper-activation in the right TPJ and MFG may reflect the process of mentalizing other person's behavior by auditory hallucination by abnormality of cognitive bias.

Keywords: attractiveness, auditory hallucinations, schizophrenia, greeting, cerebral laterality, social communications, functional MRI

INTRODUCTION

Auditory hallucinations and thought disorder are the main symptoms of schizophrenia, and these symptoms profoundly affect the neural basis of social communications as well as behavior (Brune et al., 2008; Bucci et al., 2008; Wible et al., 2009; Kumari et al., 2010; Granholm et al., 2012; Waters et al., 2012). In order to understand these psychiatric symptoms in schizophrenia, it is important to verify the pathophysiology of cerebral function in auditory communications.

For healthy people, greeting conversations are very essential tools for communicating socially with family, friends, and community. Since favorable greetings strengthen cordial relationships with colleagues, maintaining the skill of socializing with greeting conversations is especially significant (Gronna et al., 1999; Barry et al., 2003). One of the main cognitive models in schizophrenia proposes that hallucinations arise from impaired self-monitoring and abnormality of cognitive bias (Allen et al., 2004). Some studies indicate that schizophrenia patients tend to misapprehend inner speech as external speech by the disturbance of self-monitoring (Morrison and Haddock, 1997; Stein and Richardson, 1999; Ford et al., 2001; Allen et al., 2004). A recent study has suggested that auditory hallucination in schizophrenia may be caused by both impaired brain function in auditory processing and disturbance of attention bias toward internally generated information (Kompus et al., 2011). If patients with schizophrenia mistake unfavorable greetings through their distorted thinking while listening to favorable greetings, social isolation and emotional withdrawal could be produced. In addition, if schizophrenia patients have auditory hallucination, misjudgment of favorable/unfavorable greeting may be induced by abnormality of cognitive bias. However, it is unclear whether schizophrenia patients with auditory hallucinations have impaired abilities to differentiate between favorable and unfavorable greetings.

Functional magnetic resonance imaging (fMRI) studies in schizophrenia have investigated the neural basis of impairment of paralinguistic processing such as emotional prosody and affective vocalizations (Mitchell et al., 2004; Leitman et al., 2007, 2011; Bach et al., 2009; Dickey et al., 2010) as well as language processing (Woodruff et al., 1997; Kircher et al., 2001; Mitchell et al., 2001; Sommer et al., 2001; Schettino et al., 2010). A previous fMRI study concerning the recognition of emotional speech prosody demonstrated that temporal activation in schizophrenia patients was predominant in the left hemisphere, whereas that in normal control subjects showed right hemispheric dominance (Mitchell et al., 2004). Another fMRI study also found right-lateralized activation in healthy controls in the temporal-parietal region while listening to emotional prosody including meaningless syllables (Bach et al., 2009). In schizophrenia patients, however, this right-lateralized pattern was even more pronounced. These findings indicate that cerebral laterality for emotional prosody in schizophrenia patients could be shifted in comparison to the typical right-lateralized activation in normal control subjects.

We consider that it is important to investigate the relationship between psychiatric symptom and cerebral function in behavior social as well as emotional prosody. Especially, evaluating facial attractiveness is a favorable behavior associated with social communication (Kampe et al., 2001; Winston et al., 2007). Recent studies have demonstrated that facial attractiveness can activate doperminergic regions including amygdala and orbitofrontal cortex that are strongly related to reward prediction (Winston et al., 2007; Cloutier et al., 2008; Chatterjee et al., 2009; Tsukiura and Cabeza, 2011). Clarifying brain mechanisms in these reward systems is very important for understanding the pathophysiology of schizophrenia. A recent study has shown that in schizophrenia, the ratings of attractiveness of unfamiliar faces were significantly reduced compared to healthy subjects (Haut and MacDonald, 2010). Further, this study has demonstrated that when the patient had severe persecutory delusions, attractiveness ratings decreased (Haut and MacDonald, 2010). As well as facial perception, auditory attractiveness in schizophrenia will be a challenging research topic. A recent fMRI study in healthy subjects on auditory attractiveness has demonstrated bilateral superior temporal gyrus (STG) and inferior frontal gyrus (IFG) activates when participants judged whether voices sounded attractive or not. This study suggests that the roles of STG and IFG are essential for perceiving auditory attractiveness (Bestelmeyer et al., 2012). The regions of STG and IFG are heavily implicated in the functional anatomy of auditory hallucination. A recent meta-analysis demonstrated that schizophrenia patients with auditory hallucination had significantly increased activity in fronto-temporal areas involved in speech generation and speech perception (Jardri et al., 2011). A recent fMRI study demonstrated that cerebral activation in fronto-temporal regions is greater than in healthy individuals during AVH but lower during environmental-stimulus processing (Kompus et al., 2011). However, to our knowledge, no study has ever investigated the cerebral response to auditory attractiveness in schizophrenia.

The aim of our research is to clarify cerebral response to auditory attractiveness when patients with schizophrenia are listening to greetings. Greeting conversations are crucial to maintaining social interactions. An fMRI study of social perception indicated that the left prefrontal and left IFG were activated when the subjects judged whether two people were friends or enemies (Farrow et al., 2011). Since the recognition of friendliness and favorability is essential for greeting conversations, the patients with schizophrenia could change cerebral function due to psychiatric symptoms such as auditory hallucinations. To investigate this pathophysiology, using completely the same greetings, we compared cerebral activation when the subjects judged favorability (recognition of auditory attractiveness) and cerebral activation when the subjects judged gender (recognition of non-auditory attractiveness). Prior to the current experiment, we hypothesized that cerebral functions underlying the perception of auditory attractiveness could be impaired in STG and IFG by occurring auditory hallucination.

MATERIALS AND METHODS

SUBJECTS OF fMRI STUDY

Eighteen right-handed controls (9 males and 9 females, mean age 35.5 years, $SD = 8.6$) and 18 schizophrenia patients (10 males and 8 females, mean age 35.7 years, $SD = 8.4$) participated in the present study. As for the subtypes of 18 schizophrenia patients, all patients were diagnosed with paranoid schizophrenia. All 18 patients were receiving neuroleptics (mean risperidone equivalent daily dosage = 4.7 mg, $SD = 2.2$; 9 patients, risperidone; 4 patients, olanzapine; 2 patients, haloperidol; 1 patient, quetiapine; 1 patient, sulpiride; 1 patient, perphenazine). Risperidone equivalents were calculated based on published equivalencies for atypical antipsychotics by Inagaki and Inada (2006). All 36 volunteers were native speakers of Japanese. None of the control subjects was taking alcohol or medication at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. After complete explanation of the study, written informed consent was obtained from all subjects, and the study was approved by the relevant ethics committee. Schizophrenia patients were diagnosed by MK and the attending psychiatrists on the basis of a review of their charts and a conventionally semi-structured interview (First et al., 1995). After the structural interview was performed using PANSS, the patient was synthetically diagnosed according to the diagnostic guidelines of the ICD-10: Classification of Mental and Behavioral Disorders. Exclusion criteria were current or past substance abuse and a history of alcohol-related problems, mood disorder, or organic brain disease. All patients were recruited from the outpatient unit of Asai Hospital. Mean illness duration was 12.3 ($SD = 8.0$) years. Clinical symptoms were assessed by Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Sum scores for positive and negative symptoms were calculated, with the positive symptom subscale including the following seven items: Delusion, Conceptual disorientation, Hallucinatory behavior, Excitement, Grandiosity, Suspiciousness, and Hostility. The negative symptom subscale also included seven items: Blunted affect, Emotional withdrawal, Poor rapport, Passive/apathetic social withdrawal, Difficulty in abstract thinking, Lack of spontaneity and flow of conversation, and Stereotyped thinking. The mean score of PANSS was 32.4 ($SD = 10.4$). The mean positive symptom score was 15.1 ($SD = 6.4$), mean negative symptom score was 20.7 ($SD = 6.2$), and mean score of general psychopathology was 32.3 ($SD = 7.9$). The candidates were carefully screened and standardized interviews were conducted by a research psychiatrist (MK) and the attending psychiatrists. They did not meet the criteria for any psychiatric disorders. There was no significant difference in the mean period of education between the controls and patients (mean ± *SD*; patients 13.3 ± 1.3 years, control subjects 13.0 ± 1.0 years; $p > 0.05$, *t*-test). Schizophrenia patients were 14 right-handed and 4 left-handed participants according to the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Mean (± *SD*) EHI in right-handed 14 patients was 90.4 ± 13.0. The EHI score of the 4 left-handed patients was −85, −73, −46, −46, respectively. All control subjects were right-handed, and mean (± *SD*) EHI was 96.1 ± 4.7.

RECORDED VOICE

As a sample for clarifying emotional response in voice recognition, Japanese greetings were recorded from 6 native speakers (3 males, 3 females). Ten greetings were recorded: Ohayo (Good Morning), Yah (Hi), Konnichiwa (Good Afternoon), Konbanwa (Good evening), Arigato (Thank you), Domo (Thank you), Irasshai (Welcome), Genki (How are you?), Dozo (Please), and Hisashiburi (Long time no see). These 10 greetings were recorded expressing favorable emotion (positive greeting), unfavorable emotion (negative greeting), or without emotion (neutral greeting), resulting in 180 stimuli in total. The voice was recorded using an IC recorder (Voice-Trek DS-71, Olympus) in a perfectly quiet room. In both the preliminary experiment and the fMRI experiment, all speakers were unknown to all participants.

PRELIMINARY EXAMINATION

Prior to the fMRI study, we asked 32 different control volunteers (16 males and 16 females) to judge the favorability of all 180 greetings (60 favorable, 60 non-favorable, and 60 neutral greetings) using a questionnaire with a 10-point scale. We defined "favorable" if the scale approached 10, whereas "unfavorable" if the scale approached 0. Based on the responses of the 32 subjects, greetings were considered positive if their average score was higher than 6.5. If the average score was less than 3.5, the greetings were considered negative. Neutral greetings were defined as being located within the average score range of 4.5–5.5. Based on these results, each speaker's greeting was evenly selected for the favorable, neutral, and unfavorable greetings.

INSTRUMENTS USED FOR PRESENTATION OF STIMULI

Stimuli were presented by the use of Media Studio Pro (version 6.0 Ulead Systems, Inc., Ulead Systems, Taiwan) running under Windows XP. Subjects listened to the sound stimuli through headphones attached to an air conductance sound delivery system (Commancer X6, MRI Audio System, Resonance Technology Inc., Los Angeles, CA). The average sound pressure of stimulus amplitude was kept at 80 dB.

EXPERIMENT DESIGN

The subjects listened for a total of 10 min and 40 s: 20 s of silence, 5 min of attentive listening (Part A), 20 s of silence, and 5 min of attentive listening (Part B). Part A and Part B each consisted of 60 paired greetings (30: neutral-positive, 30 neutral-negative), with each greeting taking 0.5 s, and pause of 1 s; all together, each of the 10 greetings was spoken 12 times (6 times as a neutral greeting, 3 times as a positive greeting, and 3 times as a negative greeting). In Part A, there were equal numbers of greetings by male pairs and female pairs. The subjects judged which greeting of a pair was more favorable. Using 30 neutral-positive and 30 neutral-negative pairs, we examined the degree of difference in favorability. We named Part A: Favorability Judgment Task (FJT). In Part B, 30 pairs were the same gender and 30 pairs were different gender. The subjects judged whether the speakers in each pair were the same gender or not. We named Part B: Gender Discrimination Task (GDT). The pairings of neutral-positive and neutral-negative appeared in random order (**Figure 1**).

FUNCTIONAL MRI ACQUISITION

The images were acquired with a 1.5 Tesla Signa system (General Electric, Milwaukee, Wisconsin). Functional images of 264 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level dependent (BOLD) contrast. Each volume consisted of 20 transaxial contiguous slices with a slice thickness of 6 mm to cover almost the whole brain (flip angle, 90°; time to echo [TE], 50 ms; repetition time [TR], 2.5 s; matrix, 64 × 64; field of view, 24 × 24).

IMAGE PROCESSING

Data analysis was performed with statistical parametric mapping software SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) running with MATLAB (Mathworks, Natick, Massachusetts). All volumes of functional EPI images were realigned to the first volume of each session to correct for subject motion, and the mean functional EPI image was spatially coregistered with the anatomical T1 images. The anatomical T1 image was segmented into the image of gray matter and white matter. Based on the segmented T1 image of each subject, the anatomical template of diffeomorphic anatomical registration through an exponentiated Lie algebra (DARTEL) was created (Ashburner, 2007). All realigned EPI images were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template with DARTEL template and flow field of each subject. Functional images were spatially smoothed with a 3-D isotropic Gaussian kernel (full width at half maximum of 8 mm). A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. The significance of hemodynamic changes in each condition was examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. The *t*-values were then transformed to unit normal distribution, resulting in z-scores. The models of 4 contrasts were created by event-related design during the fMRI experiments. In FJT task, 2 contrasts [30 pairs of neutral-favorable greetings (FAV) and 30 pairs of neutral-unfavorable greetings (NFV)] were made. In GDT task, 2 contrasts [30 pairs of same gender greetings (SAM) and 30 pairs of different gender greetings (DIF)] were made (**Figure 1**).

STATISTICAL ANALYSIS

Group analysis (2nd-level analysis in spm8) was performed on the data for 18 control subjects and 18 schizophrenia patients using a random effect model on a voxel-by-voxel basis. FMRI data

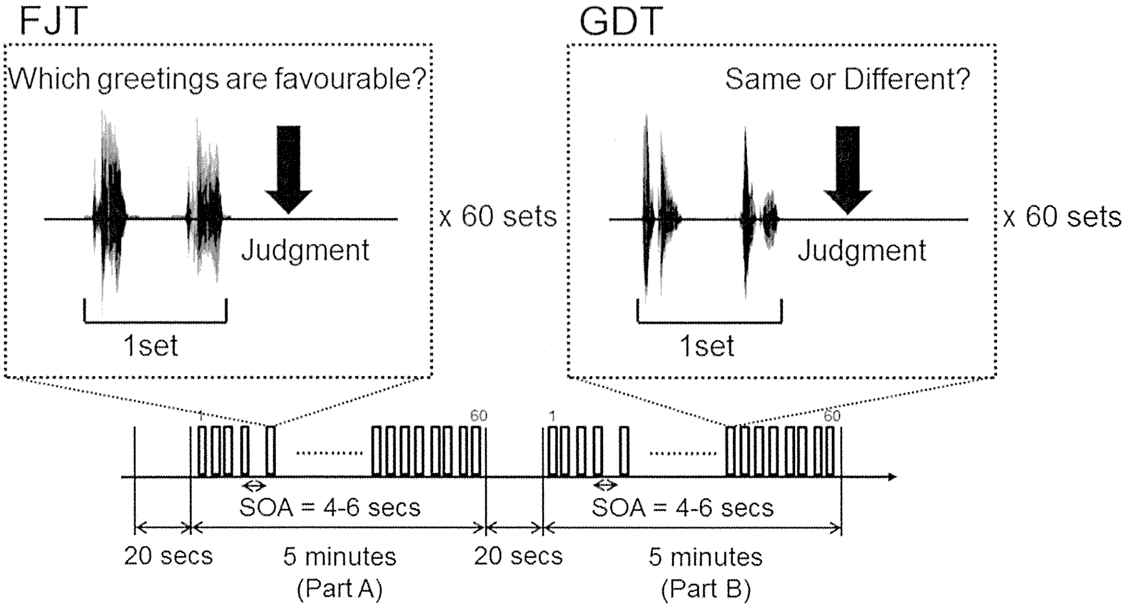


FIGURE 1 | Experimental design of fMRI Part A is Favorability Judgment Task (FJT). Part B is Gender Discrimination Task (GDT).

was analysed based on the 2 × 2 × 2 full factorial model with the factors of Group (control subjects/schizophrenia patients), Task (FJT/GDT) and Within-task (FJT: FAV/NFV, GDT: SAM/DIF) (FDR-corrected voxel-level threshold of $P < 0.05$). By using rfx-plot (Glascher, 2009), cerebral activation at the regions of interests (ROIs) was investigated. In main effect of Group and main effect of Task, ROIs were focused on the coordinates of the peak voxel of activation under FDR-corrected voxel-level threshold of $P < 0.05$. For main effect of Group, cerebral laterality of ROIs was evaluated. In order to investigate cerebral laterality, ROIs were also set on the hemispheric symmetrical region of the MNI coordinates. By using these symmetrical ROIs, the laterality index (LI) was calculated [$\mathrm{LI} = (\mathrm{L} - \mathrm{R})/(\mathrm{L} + \mathrm{R}) \times 100$; L = beta estimates of left hemispheric activation, R = beta estimates of right hemispheric activation]. The formula of the LI was calculated based on previous studies (Koeda et al., 2006, 2007; White et al., 2009). In calculation of LI, the beta value of each subject used was either plus or zero, and minus beta values were excluded. In this ROI analysis, correlation between EHI score and beta value was evaluated to investigate the influence of handedness. Correlations between the subscores of PANSS (total scores of positive symptoms, negative symptoms, and general psychopathology) and cerebral activation under FJT vs. GDT contrast were calculated based on simple regression in schizophrenia patients. In linear regression analyses, the three subscores of PANSS were used, each with one predictor, respectively. In the analysis of full factorial design, the statistical threshold used was $p < 0.05$, voxel level, FDR-corrected. In the linear regression analysis, the statistical threshold used was $p < 0.0001$, voxel level, uncorrected (FDR < 0.25, voxel level corrected). Further, the correlation was analysed between the beta value of FJT at the specific ROIs of main effect of Group (**Figure 10**).

RESULTS

PRELIMINARY EXPERIMENTS

Favorability was rated by 32 different control volunteers using a scale of 1–10. **Figure 2** shows the distribution of the rating of favorability. Based on the definition of favorability (Materials and Methods: Preliminary Examination), 30 favorable vocalizations (rating average more than 6.5; 12 males and 9 females), 60 neutral vocalizations (rating average between 4.5 and 5.5; 17 males and 18 females), 30 unfavorable vocalizations (rating average less than 3.5; 7 males and 13 females) were selected. The mean ratings (± *SD*) of favorability were 2.3 ± 0.6 (unfavorable), 4.9 ± 0.3 (neutral), and 7.5 ± 0.6, respectively. Analysis of variance (One-Way ANOVA) was significantly different [$F_{(2,\ 117)} = 1006.9$, $p < 0.001$]. Multiple comparisons were also significant (unfavorable vs. neutral: 2.6 ± 0.1, $p < 0.001$; neutral vs. favorable: 2.6 ± 0.1, $p < 0.001$; unfavorable vs. favorable: 5.2 ± 0.1, $p < 0.001$).

Behavioral data (accuracy)

In the fMRI experiment, the mean percentages (±*SD*) of the accuracy of the control subjects for FJT and GDT were 94.7 ± 6.1% and 97.0 ± 3.1%, and those of schizophrenia patients were 90.9 ± 6.0% and 95.1 ± 4.8%, respectively (**Figure 3**). There was no significant difference between the two groups [FJT: $t_{(34)} = 1.89$, $p > 0.05$; GDT: $t_{(34)} = 1.45$, $p > 0.05$]. Mixed analysis of variance (mixed ANOVA) in the performance did not show a significant main effect of Group (control subjects/schizophrenia patients): $F_{(1,\ 34)} = 2.33$, $p > 0.05$, whereas a significant Task effect (FJT vs. GDT) was observed: $F_{(1,\ 34)} = 11.5$, $p < 0.001$. No interaction effect between Group and Task was observed: $F_{(1,\ 34)} = 0.19$, $p > 0.05$. **Table 1** shows the mean accuracy for judgment of favorable/non-favorable, and judgment of same

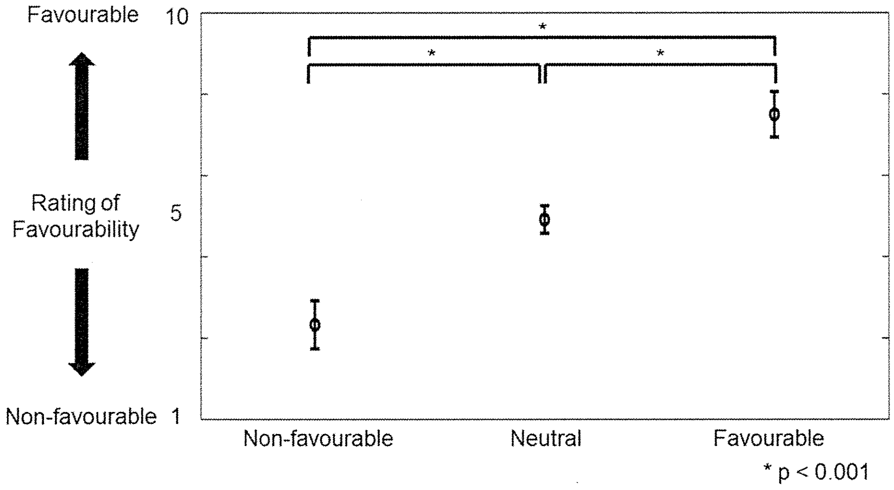


FIGURE 2 | The figure shows the distribution (mean ± *SD*) of rating favorability for portraying favorable, neutral, and unfavorable greetings in preliminary experiment. The vertical axis represents the rating score of favorability (1–10). *Indicates that multiple comparison was significant.

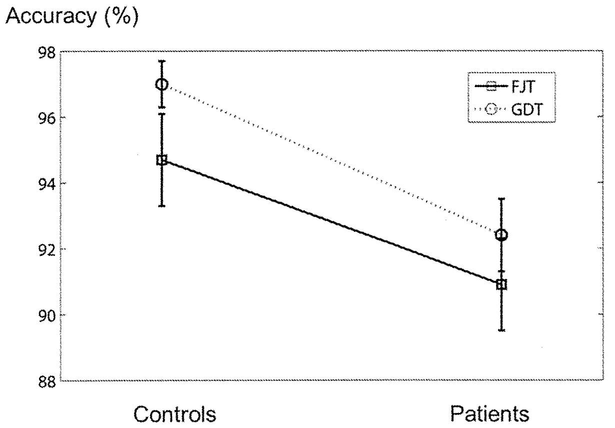


FIGURE 3 | The figure shows the error bar (mean ± *SD*) of the accuracy in the fMRI experiment. The vertical axis represents the accuracy of the experiment.

gender and different gender (FAV controls: 93.5 ± 7.6%; FAV patients: 94.1 ± 6.2%; NFV controls: 94.7 ± 6.1%; NFV patients: 90.0 ± 6.0%; SAM controls: 98.3 ± 2.4%; SAM patients: 95.7 ± 5.6%; DIF controls: 97.2 ± 3.8%; DIF patients: 95.0 ± 4.2%). No significant difference was observed between controls and patients [FAV: $t_{(34)} = -0.24$, $p > 0.05$; NFV: $t_{(34)} = 1.89$, $p > 0.05$; SAM: $t_{(34)} = 1.82$, $p > 0.05$; DIF: $t_{(34)} = 1.67$, $p > 0.05$]. Three-Way ANOVA was calculated for the effect of Group, Task, and Within-task. Task effect was significantly observed [$F_{(1,\ 34)} = 11.9$, $p = 0.002$], whereas Group effect and Within-task effect were not observed [Group: $F_{(1,\ 34)} = 2.33$, $p > 0.05$; Within-task: $F_{(1,\ 34)} = 2.55, p > 0.05$]. Interaction effect was not observed in the effect of Group × Task [$F_{(1,\ 34)} = 0.17$, $p > 0.05$] and the effect of Group × Within-task [$F_{(1,\ 34)} = 2.80$, $p > 0.05$].

Response time

The mean (± *SD*) response times relative to offset of stimulus (seconds) of control subjects and schizophrenia patients for FJT and GDT were the following: FJT-control: 2.41 ± 0.78 s, FJT-patients: 2.01 ± 0.33 s, GDT-control: 2.15 ± 0.78 s, and GDT-patients 1.99 ± 0.05 s. The response times in FJT were significantly different between control subjects and schizophrenia patients: $t_{(34)} = 2.16, p = 0.04 < 0.05$, whereas there was no significant difference in the response times to GDT: $t_{(34)} = 0.84$ $p > 0.05$. Analysis of variance on the response time was performed with the factors of Group (control subjects/schizophrenia patients) and Task (FJT/GDT). There was no significant difference between Groups: $F_{(1,\ 34)} = 2.29$, $p > 0.05$, whereas there was a significant Task effect: $F_{(1,\ 34)} = 33.7$, $p < 0.001$. An interaction effect between Group and Task was also observed: $F_{(1,\ 34)} = 24.4$, $p < 0.001$. **Table 1** (lower part) shows the mean response time for judgment of favorable/non-favorable, and judgment of same gender and different gender [FAV controls: 2.41 ± 0.78 s; FAV patients: 2.17 ± 0.17 s; NFV controls: 2.01 ± 0.13 s; NFV patients: 1.89 ± 0.15 s; SAM controls: 2.15 ± 0.78 s; SAM patients: 1.93 ± 0.14 s; DIF controls: 1.99 ± 0.53 s; DIF patients: 2.07 ± 0.13 s]. Significant difference between controls and patients was observed in NFV and DIF [NFV: $t_{(18.4)} = 3.49$, $p > 0.05$; DIF: $t_{(22.8)} = -2.31, p < 0.05$: Welch's *t*-test], whereas no significant difference was observed in FAV and SAM [FAV: $t_{(18.6)} = 1.29, p > 0.05$; SAM: $t_{(18.1)} = 1.15, p > 0.05$: Welch's *t*-test]. Three-Way ANOVA was calculated for the effect of Group, Task, and Within-task. Task effect was significantly observed [$F_{(1,\ 34)} = 36.7$, $p < 0.001$], whereas Group effect and Within-task effect were not observed [Group: $F_{(1,\ 34)} = 1.93, p > 0.05$; Within-task: $F_{(1,\ 34)} = 0.13, p > 0.05$]. Interaction effect was significantly observed in the effect of Group × Task [$F_{(1,\ 34)} = 16.0, p < 0.001$], whereas interaction effect was not significantly observed in the effect of Group × Within-task [$F_{(1,\ 34)} = 1.04$; $p > 0.05$].

Table 1 | Shows the mean ± *SD* of accuracy and response time in fMRI experiments.

		FAV	NFV	SAM	DIF
Accuracy (%)	Controls	93.5 ± 7.6	94.7 ± 6.1	98.3 ± 2.4	97.2 ± 3.8
	Patients	94.1 ± 6.2	90.9 ± 6.0	95.7 ± 5.6	95.0 ± 4.2
Response time (sec)	Controls	2.41 ± 0.78	2.01 ± 0.13	2.15 ± 0.78	1.99 ± 0.53
	Patients	2.17 ± 0.17	1.89 ± 0.15	1.93 ± 0.14	2.07 ± 0.13

FAV, pairs of neutral-favorable greetings; NFV, pairs of neutral-unfavorable greetings; SAM, pairs of same gender greetings; DIF, pairs of different gender greetings.

FUNCTIONAL MRI DATA

Full factorial design analysis

FMRI data was analysed based on the $2 \times 2 \times 2$ full factorial model with the three factors: Group (control subjects/schizophrenia patients), Task (FJT/GDT), and Within-task (FJT: FAV/NFV, GDT: SAM/DIF) (FDR-corrected voxel-level threshold of $P < 0.05$).

Main effect of Group was significantly observed in the bilateral middle frontal gyrus (MFG), left STG, right superior parietal lobe (SPL) temporo-parietal junction (TPJ), right occipital lobe, and right amygdala ($p < 0.05$, FDR-corrected, **Figure 4** and **Table 2**). The upper part (gray bar) of **Figure 4** shows the bar graph for contrast estimates and 90% confidence interval in each activated region (gray bar: controls, the light gray bar: patients). From the results of main effect of Group, ROIs were set on the 5 regions: left MFG [−26, −3, 62], right amygdala [20, −3, 21], left STG [−54, −21, 3], right TPJ [26, −65, 53], and right occipital lobe [8, −77, 2]. In these ROIs, Mann–Whitney test was calculated for beta values between controls and patients. The P-threshold was Bonferroni-corrected based on 5 tests being conducted. Cerebral activation in left STG was significantly greater in control subjects than in schizophrenia patients (L STG: $z = 3.10$, $p = 0.001 < 0.05/5$), whereas cerebral activations in the other regions were significantly greater in schizophrenia patients than in control subjects (L MFG: $z = -3.61$, $p < 0.05/5$; R amygdala: $z = -3.54$, $p < 0.05/5$; R TPJ: $z = -3.61$, $p < 0.05/5$; R occipital: $z = -3.54$, $p < 0.05/5$). In these 5 ROIs and contralateral symmetrical 5 ROIs (right MFG [26, −3, 62], left amygdala [−20, −3, 21], right STG [54, −21, 3], left TPJ [−26, −65, 53], left occipital lobe [−8, −77, 2]), cerebral activation under FAV, NFV, SAM, and DIF conditions was evaluated (middle part of **Figure 4**). Further, the LI was calculated (lower part of **Figure 4**). For each ROI, Two-Way ANOVA was calculated by main effect of Group and Within-task. Regarding Group effect, in the ROIs at the bilateral MFG, bilateral amygdala, bilateral TPJ, and right occipital lobe, the strength of BOLD signal (beta estimates) in patients under the FAV and NFV conditions was significantly greater than that in controls [L MFG: $F_{(1,\,34)} = 14.1, p < 0.001$; R MFG: $F_{(1,\,34)} = 21.5, p < 0.001$; L amygdala: $F_{(1,\,34)} = 14.9, p < 0.001$; R amygdala: $F_{(1,\,34)} = 18.0$, $p < 0.001$; L TPJ: $F_{(1,\,34)} = 12.7$, $p < 0.001$; R TPJ: $F_{(1,\,34)} = 4.67$, $p < 0.05$; R occipital: $F_{(1,\,34)} = 14.4, p < 0.001$], whereas that in bilateral STG was significantly greater in controls than in patients [L STG: $F_{(1,\,34)} = 12.7$, $p < 0.001$; R STG: $F_{(1,\,34)} = 4.7$, $p < 0.05$]. In bilateral MFG, right amygdala, and right occipital, BOLD signals of patients under SAM and DIF conditions were significantly greater than in controls [L MFG: $F_{(1,\,34)} = 14.1$, $p < 0.001$; R MFG: $F_{(1,\,34)} = 21.5$, $p < 0.001$; R amygdala: $F_{(1,\,34)} = 7.8$, $p < 0.01$; R occipital: $F_{(1,\,34)} = 5.9$, $p < 0.05$]. Significant difference of LI was observed in the amygdala and occipital lobe under SAM and DIF conditions [amygdala LI: $F_{(1,\,34)} = 7.8$, $p < 0.001$; occipital lobe: $F_{(1,\,34)} = 6.5$, $p < 0.05$], whereas significant difference in the other regions was not observed ($p > 0.05$).

Main effect of Task (FJT/GDT) was significantly observed in the left precentral gyrus (PrCG), left MFG, left IFG, right insula, bilateral STG, left claustrum, and left cerebellum ($p < 0.05$, FDR-corrected, **Figure 5** and **Table 3**). Cerebral activation in the left IFG and bilateral STG was significantly greater in FJT than in GDT [**Figure 5**; L IFG: $t_{(70)} = 3.92$, $p < 0.05/6$; L STG: $t_{(70)} = 4.64, p < 0.05/6$; R STG: $t_{(70)} = 2.92, p = 0.005 < 0.05/6$]. Interaction effect between Group and Task was not significantly observed at a threshold of $p < 0.05$, FDR-corrected.

CORRELATION BETWEEN PSYCHIATRIC SYMPTOM AND CEREBRAL ACTIVATION

We examined correlations between PANSS and cerebral activation under FJT minus GDT contrast. Significant positive correlations were observed in the right superior frontal gyrus (SFG), right MFG, left IFG, left STG, and right IPL in schizophrenia ($p < 0.25$, FDR-corrected, **Figure 6** and **Table 4**). **Figure 7** demonstrated correlations between the severity of auditory hallucinations and cerebral activation under FJT minus GDT contrast. Significant positive correlations were observed in the right post central gyrus (PsCG), right PrCG, right MFG and right IPL in schizophrenia ($p < 0.25$, FDR-corrected, **Figure 7** and **Table 5**).

CORRELATION BETWEEN HANDEDNESS AND CEREBRAL ACTIVATION

We examined the correlation between handedness and cerebral activation. The beta value of ROI analysis in main effect of Group was used in this analysis. Cerebral activations in most ROIs were not correlated with the handedness score, but activation in STG was significantly negatively correlated with the handedness score (**Figure 8**). In the ROI of STG, differences in LI between 18 controls and 14 patients were analysed after removing 4 left-handed patients. However, significant difference in the LI was not observed.

CORRELATION BETWEEN ACCURACY OF TASK AND CEREBRAL ACTIVATION

In the ROIs of main effect of Group, correlation was analysed between the beta value of FJT at left STG and accuracy.

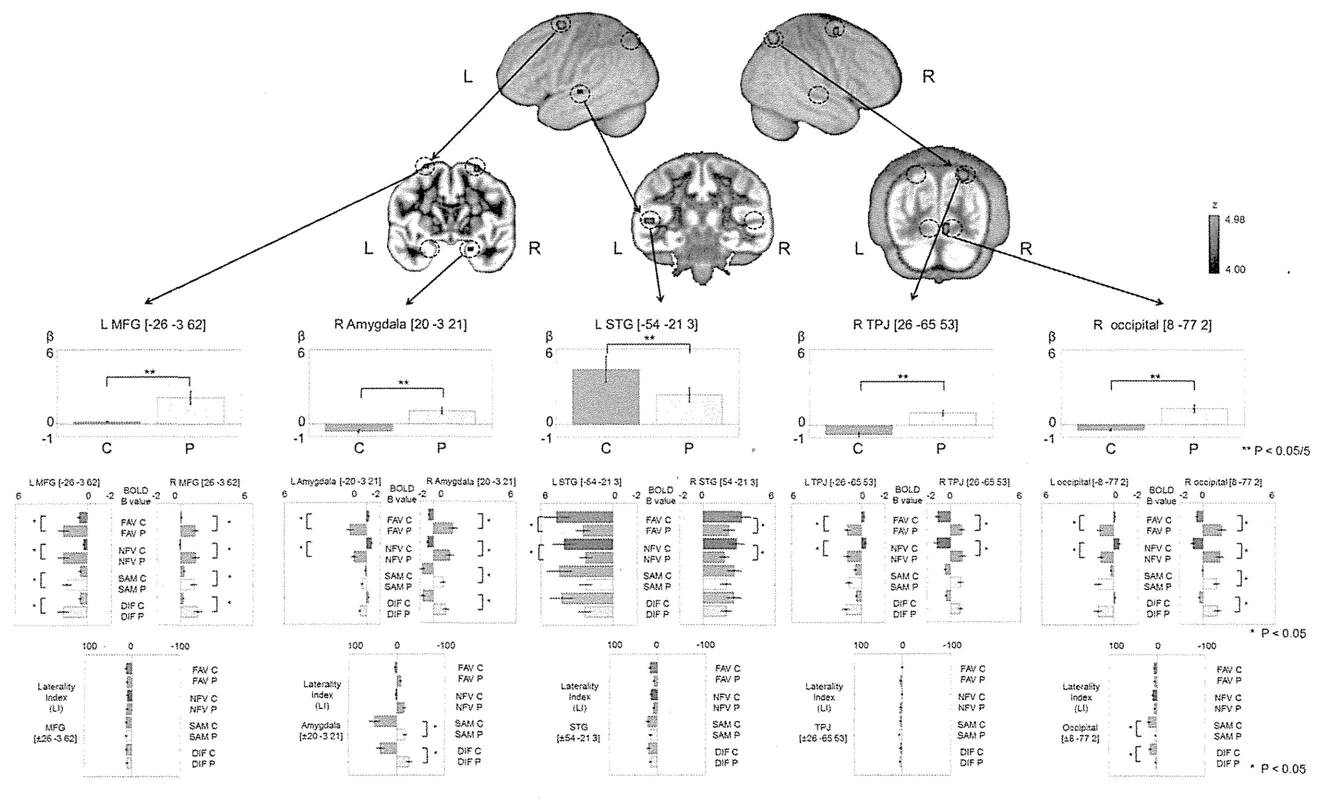


FIGURE 4 | The figure demonstrates the results of main effect of Group (controls/patients) in analysis of 2 × 2 × 2 full factorial design. Upper pictures show cerebral activation on main effect of Group ($p < 0.05$, voxel level, FDR-corrected). Gray bars in the upper row represent the distribution of beta values (mean ± SE) in controls (dark gray color) and patients (light gray color). The vertical axis, beta values; C, controls; P, patients; L, left; R, right. **Indicates $p < 0.05/5$ (Bonferroni correction by 5 ROIs). Color bars in the middle row represent the distribution of beta values (mean ± SE) on 5 ROIs and contralateral symmetrical 5 ROIs under FAV (red), NFV (blue), SAM (gray), and DIF (green) conditions—C, controls (dark gray); P, patients (light gray). Color bars at the bottom represent the distribution of laterality index (mean ± SE) on the 5 ROIs. *Indicates $p < 0.05$. MFG, middle frontal gyrus; STG, superior temporal gyrus; TPJ, temporo-parietal junction; occipital, occipital lobe.

Table 2 | Peak coordinates (*x*, *y*, *z*) and their *z*-values of cerebral activation by full factorial design analysis with Group effect (controls and patients).

Brain regions	*BA*	Coordinate			$F_{(1, 136)}$	*z*-value	*P* (FDR-corrected)
		x	*y*	*z*			
MAIN EFFECT OF GROUP (CONTROLS/SCHIZOPHRENIA)							
Controls > Patients							
L STG	41	−54	−21	3	23.20	4.47	<0.05
Patients > Controls							
L MFG	6	−26	−1	63	23.40	4.49	<0.05
R MFG	6	27	−1	61	19.50	4.10	<0.05
R SPL	7	26	−64	52	29.70	5.04	<0.05
Occipital lobe	18	8	−76	1	21.80	4.34	<0.05
R amygdala		20	−3	−21	18.40	3.99	<0.05

L, left hemisphere; R, right hemisphere; p < 0.05, voxel level, FDR-corrected.

A significantly positive correlation was observed ($r = 0.346$, $p < 0.05$, **Figure 10**). The other areas were not significantly correlated with accuracy. These findings suggest that the less the accuracy is, the less the beta value of FJT at left STG is.

DISCUSSION

To clarify cerebral function underlying the perception of voice attractiveness including greeting conversations in patients with schizophrenia, we investigated the difference of cerebral

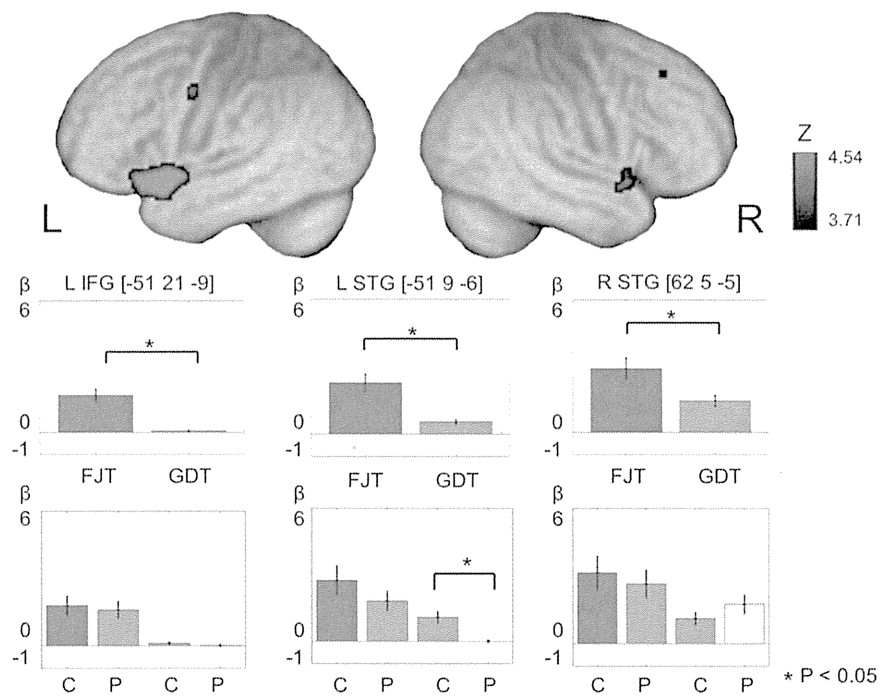


FIGURE 5 | The figure represents cerebral activation on main effect of task [(FJT/GDT): $p < 0.05$, voxel level, FDR-corrected]. Color bars show the distribution of beta values (mean ± *SD*) under FJT (red) and GDT (gray). *Indicates $p < 0.05$—L, left; R, right; dark color, controls; light color, patients.

Table 3 | Peak coordinates (*x*, *y*, *z*) and their *z*-values of cerebral activation by full factorial design analysis with task effect (controls and patients).

Brain regions	*BA*	Coordinate			$F_{(1, 136)}$	*z*-value	*P* (FDR-corrected)
		x	*y*	*z*			
MAIN EFFECT OF TASKS (FJT/GDT)							
L PrCG	6	−50	−4	42	18.50	4.00	<0.05
R MFG	8	27	27	43	16.00	3.70	<0.05
L IFG	47	−51	21	−9	23.90	4.54	<0.05
R insula	13	38	5	−3	19.70	4.13	<0.05
L STG	22	−59	9	−2	30.80	5.13	<0.05
R STG	22	62	5	−5	19.00	4.05	<0.05
L Claustrum		−36	−10	−2	22.20	4.39	<0.05
L cerebellum		−12	−43	−21	20.20	4.13	<0.05

L, left hemisphere; R, right hemisphere; $p < 0.05$, voxel level, FDR-corrected.

activation between control subjects and schizophrenia patients while they were judging favorability or gender of vocalizations. In our present experiment, the left IFG-STG was activated in the processing of favorability judgment in both controls and schizophrenia patients. Although cerebral activation in the left STG was reduced in schizophrenia, cerebral activation in the right MFG, right IPL, and right amygdala was increased. Further, by correlation analysis between psychiatric symptom and cerebral activation of favorability, we confirmed that positive and negative symptoms in schizophrenia are closely related to cerebral dysfunction in the left STG and right MFG-IPL (**Figure 9**).

FRONTOTEMPORAL FUNCTION TO AUDITORY ATTRACTIVENESS AND ITS DYSFUNCTION IN SCHIZOPHRENIA

Our results by full factorial design also exhibited main effect of experimental Task (FJT/GDT) in the left STG and left IFG (**Figure 5**, **Table 3**). Recent auditory fMRI studies demonstrated that the cerebral function of STS is important to grasp auditory social cues (Saarela and Hari, 2008; Scharpf et al., 2010). Further, a recent fMRI study concerning auditory attractiveness demonstrated the importance of the functional connection between STG and IFG (Bestelmeyer et al., 2012). In accord with these findings, our results showed left STG-IFG activation in the recognition of auditory attractiveness including social communications.

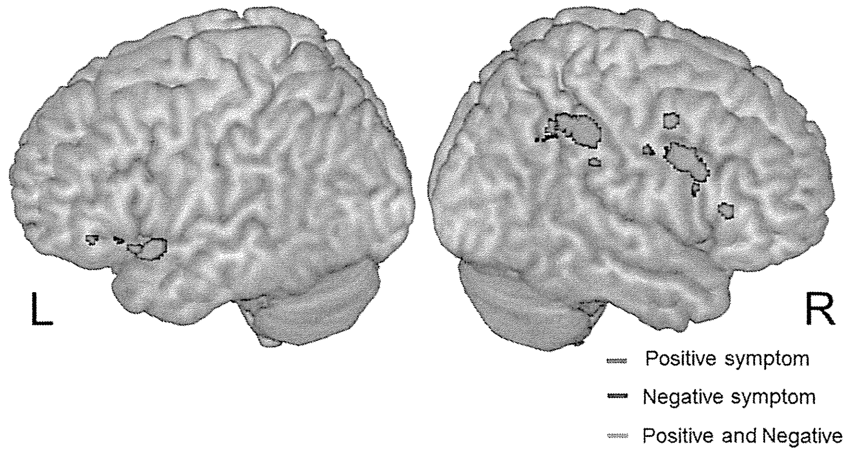


FIGURE 6 | Positive correlation between psychiatric symptom and cerebral activation under FJT > GDT contrast (univariate analysis). Positive symptom is red color, Negative symptom is blue color. Purple color indicates both symptoms. Statistical threshold: $p < 0.25$, FDR-corrected; L, left; R, right side.

Table 4 | Positive correlation between PANSS and cerebral activation under FJT minus GDT, $p < 0.0001$ uncorrected ($p < 0.25$, FDR-corrected), R, right hemisphere.

Brain regions	*BA*	Coordinate			*z*-value	*P* (uncorrected)	*P* (FDR-corrected)
		x	*y*	*z*			
L SFG	6	−6	9	55	3.73	<0.0001	<0.25
R SFG	6	9	8	60	4.04	<0.0001	<0.25
R MFG	9	51	6	36	3.77	<0.0001	<0.25
L STG	38	−50	12	−8	3.72	<0.0001	<0.25
R IPL	40	40	−43	49	4.16	<0.0001	<0.25

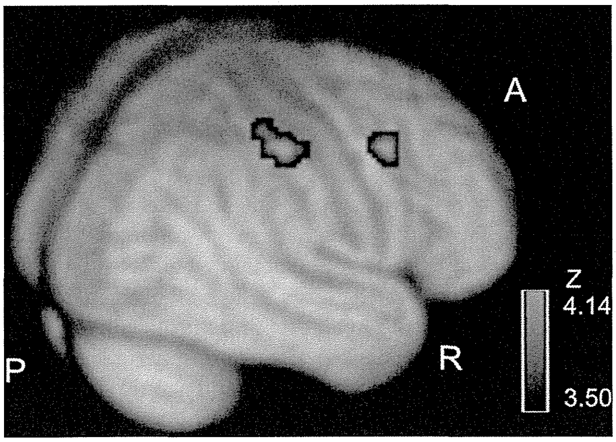


FIGURE 7 | Positive correlation between severity of hallucinatory behavior and cerebral activation under FJT > GDT contrast. Purple color bar shows *z*-value. Statistical threshold: $p < 0.25$, FDR-corrected; R, right; A, anterior; P, posterior.

Before the experiment, we hypothesized that left STG-IFG activation by auditory attractiveness could be impaired in schizophrenia. Predictably, cerebral activation in schizophrenia patients was greater in the bilateral prefrontal regions in comparison with control subjects (**Figure 5**). A recent study indicated that brain activity in the left prefrontal regions reflected the overall perceived attractiveness of the voices (Bestelmeyer et al., 2012). Further, another fMRI study indicated that the left ventrolateral prefrontal cortex, bilateral dorsal IFG, and medial frontal cortex are activated when the subjects judged whether pairs of human individuals were friends or enemies (Farrow et al., 2011). These reports indicate that prefrontal regions are associated with the judgment of favorability and friendliness. In our present study, hyper-frontality and hypo-temporality in schizophrenia patients could designate the dysfunction of left STG-IFG when they judged favorability.

In our study, cerebral activation to favorability judgment was reduced in the left STG, while it was increased in the MFG, amygdala, TPJ, and occipital lobe in the right hemisphere. A recent fMRI study suggested that paradoxical brain activation in schizophrenia patients with auditory hallucination may be caused by both reduced activation due to impaired brain function in auditory processing and increased activation due to disturbance of attention bias toward internally generated information (Jardri et al., 2011; Kompus et al., 2011). In accordance with this recent study, less activation in schizophrenia could represent impairment of favorability judgment in auditory processing, whereas greater activation in schizophrenia may reflect disturbance of attention bias toward

Table 5 | Positive correlation between the severity of hallucinatory behavior and cerebral activation under FJT minus GDT, $p < 0.0001$ uncorrected ($p < 0.25$, FDR-corrected), R, right hemisphere.

Brain regions	*BA*	Coordinate			*z*-value	*P* (uncorrected)	*P* (FDR-corrected)
		x	*y*	*z*			
CORRELATION OF HALLUCINATORY BEHAVIOR							
R PsCG	2	48	−19	30	4.55	<0.0001	<0.25
R PrCG	6	46	−16	30	4.10	<0.0001	<0.25
R MFG	9	48	8	42	3.72	<0.0001	<0.25
R IPL	40	45	−33	46	4.14	<0.0001	<0.25

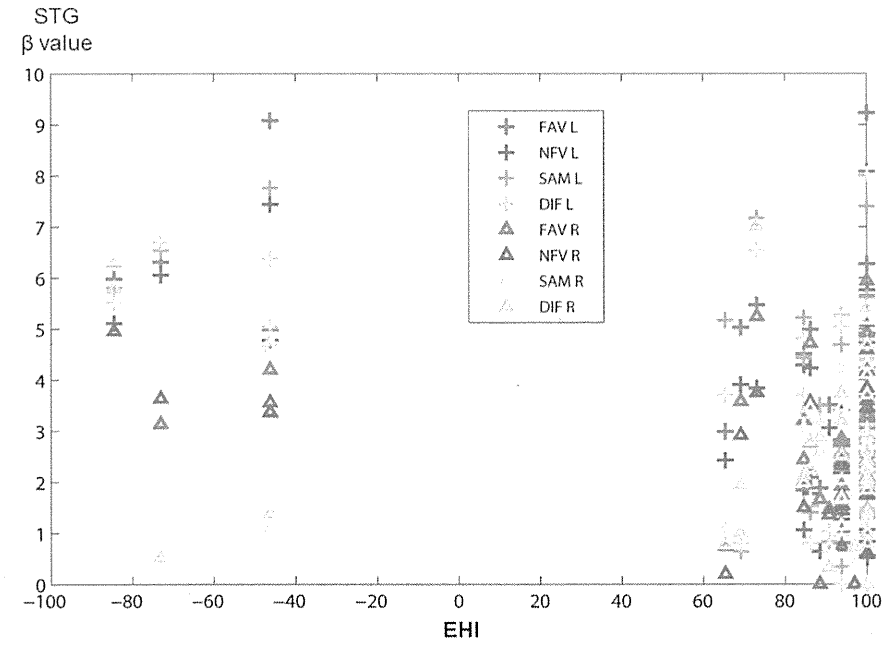


FIGURE 8 | The figure shows the distribution of correlations between activation in STG (in main effect of Group) and handedness score (EHI) in all participants. The vertical axis shows beta value in STG, and the horizontal axis shows EHI score (−100 represents extremely left-handed; 100 represents extremely right-handed). Plus marks, left hemisphere; triangles, right hemisphere; FAV (red), NFV (blue), SAM (gray), DIF (green).

internally generated information by the appearance of auditory hallucination.

CEREBRAL LATERALITY TO AUDITORY ATTRACTIVENESS IN SCHIZOPHRENIA

Interestingly, our results in schizophrenia patients exhibited enhanced right-lateralization to auditory attractiveness mainly in MFG and IPL (**Figure 4**). Previous fMRI studies concerning language processing have demonstrated that schizophrenia patients show either reduced left hemispheric activation (Kiehl and Liddle, 2001; Kircher et al., 2001; Koeda et al., 2006) or reversed language dominance (Woodruff et al., 1997; Menon et al., 2001; Ngan et al., 2003; Bleich-Cohen et al., 2009). Conversely, previous fMRI studies concerning non-linguistic processing in schizophrenia indicated reduced right hemispheric activation (Koeda et al., 2006), reversed right-lateralized activation (Mitchell et al., 2004), or enhanced right-lateralized activation (Bach et al., 2009). In accordance with the latter report, our results showed greater right prefrontal and inferior parietal activation during favorability judgment in schizophrenia (**Figure 4**). In the analysis by full factorial design, main effect of Group (controls/patients) revealed greater activation of schizophrenia in the right hemisphere compared with controls (**Figure 4**). This result also indicates enhanced right hemispheric activation by auditory attractiveness in schizophrenia. It could be speculated that these strong right hemispheric activations compensate the dysfunction of left STG-IFG related to auditory attractiveness (**Figure 4**).

PSYCHIATRIC SYMPTOMS AND AUDITORY ATTRACTIVENESS IN SCHIZOPHRENIA

Our results revealed a positive correlation between psychiatric symptom (total PANSS score, positive and negative symptom) and cerebral activation under FJT vs. GDT contrast at left STG-IFG and right prefrontal and superior/inferior parietal cortex (**Figure 6** and **Table 4**). In both positive and negative symptoms,

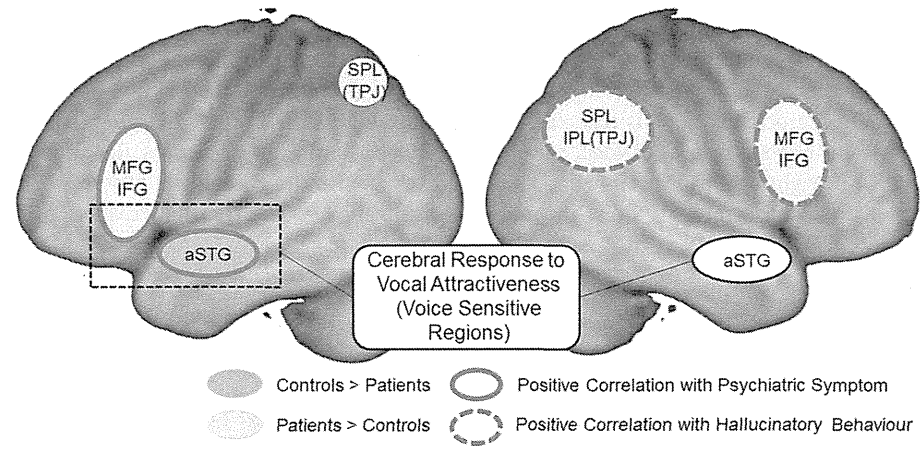


FIGURE 9 | Summary of cerebral response to auditory attractiveness and psychiatric symptom in schizophrenia: red circle shows the area of positive correlation between cerebral activation and total PANSS score; red dashed line shows the area of positive correlation between cerebral activation and hallucinatory behavior; light blue area represents greater activation in patients than in controls; pink area represents less activation in patients than in controls. MFG, middle frontal gyrus; IFG, inferior frontal gyrus; aSTG, anterior superior temporal gyrus; SPL, superior parietal lobe; TPJ, temporo-parietal junction; IPL, inferior parietal lobe.

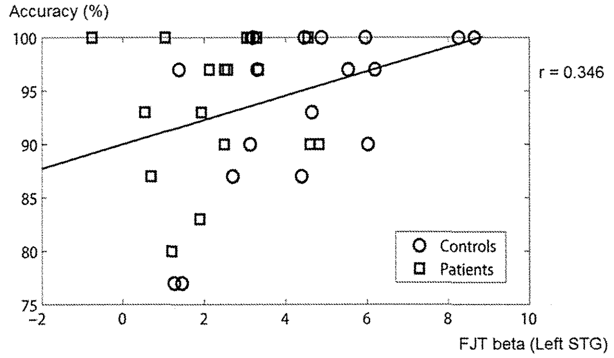


FIGURE 10 | Correlation between beta value of FJT at left STG and accuracy. The circles show control subjects. The rectangles show schizophrenia patients.

almost the same regions were correlated with cerebral activation for auditory attractiveness. Left STG-IFG activation was observed in the favorability judgment (**Figure 5**). These findings could be considered to reflect the dysfunction of the left STG-IFG region in the recognition of auditory attractiveness. Crucially, cerebral activation in the right prefrontal and superior/inferior parietal region was positively correlated with the severity of auditory hallucination (**Figure 7**, **Table 5**). These areas also demonstrated greater activation under FJT vs. GDT contrast in schizophrenia (**Figure 5**, **Table 3**). These findings indicate that greater activation to the favorability judgment in schizophrenia is related to severity of auditory hallucinations. Previous studies indicate that the right MFG/IFG-IPL region is closely related to self-referential processing (Fossati et al., 2003; Canessa et al., 2005; Uddin et al., 2005). Especially, one study demonstrated that right fronto-parietal regions as well as left prefrontal and parietal regions were activated when subjects understood the context related to social communications when two persons exchange goods, i.e., if you give me one, I will give you the other (Canessa et al., 2005). Further, another study exhibited that right dorsal IFG was activated in the processing of social alliance (friendliness) (Farrow et al., 2011). These previous findings support that the right MFG/IFG-IPL region associates with the recognition of social communications such as judgment of favorability. These activations could be attributed to representing the dysfunction of the fronto-parietal region in the processing of social communications by auditory hallucinations.

Recent fMRI studies investigated cerebral function when the subjects mentalize the other person's thoughts and behavior. These reports indicate that the role of the temporal-parietal junction is closely associated with comprehending the mental states of others (Siegal and Varley, 2002; Finger et al., 2006; Shamay-Tsoory et al., 2006; David et al., 2008). A recent study investigated cerebral activation in the processing of self-other distinction. This study demonstrated that the increase in cerebral activation in the right IPL correlated positively with the strength of psychiatric symptoms in schizophrenia (Jardri et al., 2011). Further, recent studies of schizophrenia reported that functional connectivity in the fronto-temporal network was decreased when the subjects comprehended the behavior of the other person (Das et al., 2012), or when the subjects listening to the other person's speech compared it with self-generated speech (Mechelli et al., 2007). Findings of greater right prefrontal-parietal activation (**Figure 4**) in schizophrenia may reflect brain activation due to comprehending other person's mental states through auditory hallucination as well as dysfunction of the fronto-temporal region in perception of vocal attractiveness.

In summary, when cerebral function in auditory attractiveness including social conversations was investigated, cerebral activation was revealed in the left STG and left IFG. Particularly, in schizophrenia, less activation was observed at the left STG compared with control subjects. In addition, greater activation in schizophrenia was confirmed in the right fronto-parietal region. Further, cerebral response in this region was correlated with the severity of auditory hallucinations. These findings suggest that dysfunction in the left fronto-temporal regions is related to the ability to appropriately assess the attractiveness of vocal communications in schizophrenia. The right fronto-parietal region could offset cerebral dysfunction to auditory attractiveness including social communications.

ACKNOWLEDGMENTS

We gratefully acknowledge the staff of Asai Hospital and Nippon Medical School Hospital; Section of Biofunctional Informatics, Tokyo Medical and Dental University; and Voice Neurocognition Laboratory, University of Glasgow. This work was supported by a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H22-seishin-ippan-002) from the Japanese Ministry of Health, Labor and Welfare.

REFERENCES

Allen, P. P., Johns, L. C., Fu, C. H., Broome, M. R., Vythelingum, G. N., and McGuire, P. K. (2004). Misattribution of external speech in patients with hallucinations and delusions. *Schizophr. Res.* 69, 277–287.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95–113.

Bach, D. R., Herdener, M., Grandjean, D., Sander, D., Seifritz, E., and Strik, W. K. (2009). Altered lateralisation of emotional prosody processing in schizophrenia. *Schizophr. Res.* 110, 180–187.

Barry, T. D., Klinger, L. G., Lee, J. M., Palardy, N., Gilmore, T., and Bodin, S. D. (2003). Examining the effectiveness of an outpatient clinic-based social skills group for high-functioning children with autism. *J. Autism Dev. Disord.* 33, 685–701.

Bestelmeyer, P. E., Latinus, M., Bruckert, L., Rouger, J., Crabbe, F., and Belin, P. (2012). Implicitly perceived vocal attractiveness modulates prefrontal cortex activity. *Cereb. Cortex* 22, 1263–1270.

Bleich-Cohen, M., Hendler, T., Kotler, M., and Strous, R. D. (2009). Reduced language lateralization in first-episode schizophrenia: an fMRI index of functional asymmetry. *Psychiatry Res.* 171, 82–93.

Brune, M., Lissek, S., Fuchs, N., Witthaus, H., Peters, S., Nicolas, V., et al. (2008). An fMRI study of theory of mind in schizophrenic patients with "passivity" symptoms. *Neuropsychologia* 46, 1992–2001.

Bucci, S., Startup, M., Wynn, P., Baker, A., and Lewin, T. J. (2008). Referential delusions of communication and interpretations of gestures. *Psychiatry Res.* 158, 27–34.

Canessa, N., Gorini, A., Cappa, S. F., Piattelli-Palmarini, M., Danna, M., Fazio, F., et al. (2005). The effect of social content on deductive reasoning: an fMRI study. *Hum. Brain Mapp.* 26, 30–43.

Chatterjee, A., Thomas, A., Smith, S. E., and Aguirre, G. K. (2009). The neural response to facial attractiveness. *Neuropsychology* 23, 135–143.

Cloutier, J., Heatherton, T. F., Whalen, P. J., and Kelley, W. M. (2008). Are attractive people rewarding? Sex differences in the neural substrates of facial attractiveness. *J. Cogn. Neurosci.* 20, 941–951.

Das, P., Calhoun, V., and Malhi, G. S. (2012). Mentalizing in male schizophrenia patients is compromised by virtue of dysfunctional connectivity between task-positive and task-negative networks. *Schizophr. Res.* 140, 51–58.

David, N., Aumann, C., Santos, N. S., Bewernick, B. H., Eickhoff, S. B., Newen, A., et al. (2008). Differential involvement of the posterior temporal cortex in mentalizing but not perspective taking. *Soc. Cogn. Affect. Neurosci.* 3, 279–289.

Dickey, C. C., Morocz, I. A., Minney, D., Niznikiewicz, M. A., Voglmaier, M. M., Panych, L. P., et al. (2010). Factors in sensory processing of prosody in schizotypal personality disorder: an fMRI experiment. *Schizophr. Res.* 121, 75–89.

Farrow, T. F., Jones, S. C., Kaylor-Hughes, C. J., Wilkinson, I. D., Woodruff, P. W., Hunter, M. D., et al. (2011). Higher or lower? The functional anatomy of perceived allocentric social hierarchies. *Neuroimage* 57, 1552–1560.

Finger, E. C., Marsh, A. A., Kamel, N., Mitchell, D. G., and Blair, J. R. (2006). Caught in the act: the impact of audience on the neural response to morally and socially inappropriate behavior. *Neuroimage* 33, 414–421.

First, M. B., Spitzer, R. L., Gibbon, M., and Williams, J. B. W. (1995). *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2.* New York, NY: Biometrics Research, New York State Psychiatric Institute.

Ford, J. M., Mathalon, D. H., Kalba, S., Whitfield, S., Faustman, W. O., and Roth, W. T. (2001). Cortical responsiveness during talking and listening in schizophrenia: an event-related brain potential study. *Biol. Psychiatry.* 50, 540–549.

Fossati, P., Hevenor, S. J., Graham, S. J., Grady, C., Keightley, M. L., Craik, F., et al. (2003). In search of the emotional self: an fMRI study using positive and negative emotional words. *Am. J. Psychiatry* 160, 1938–1945.

Glascher, J. (2009). Visualization of group inference data in functional neuroimaging. *Neuroinformatics* 7, 73–82.

Granholm, E., Ben-Zeev, D., Link, P. C., Bradshaw, K. R., and Holden, J. L. (2012). Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. *Schizophr. Bull.* 38, 414–425.

Gronna, S. S., Serna, L. A., Kennedy, C. H., and Prater, M. A. (1999). Promoting generalized social interactions using puppets and script training in an integrated preschool. A single-case study using multiple baseline design. *Behav. Modif.* 23, 419–440.

Haut, K. M., and MacDonald, A. W. 3rd. (2010). Persecutory delusions and the perception of trustworthiness in unfamiliar faces in schizophrenia. *Psychiatry Res.* 178, 456–460.

Inagaki, A., and Inada, T. (2006). The 18th 'Antipsychotic Equivalent Doses' (2006 version). *Rinsho Seishin-Yakuri* 9, 1443–1447.

Jardri, R., Pins, D., Lafargue, G., Very, E., Ameller, A., Delmaire, C., et al. (2011). Increased overlap between the brain areas involved in self-other distinction in schizophrenia. *PLoS ONE* 6:e17500. doi: 10.1371/journal.pone.0017500

Kampe, K. K., Frith, C. D., Dolan, R. J., and Frith, U. (2001). Reward value of attractiveness and gaze. *Nature* 413, 589.

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.

Kiehl, K. A., and Liddle, P. F. (2001). An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia. *Schizophr. Res.* 48, 159–171.

Kircher, T. T., Liddle, P. F., Brammer, M. J., Williams, S. C., Murray, R. M., and McGuire, P. K. (2001). Neural correlates of formal thought disorder in schizophrenia: preliminary findings from a functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* 58, 769–774.

Koeda, M., Takahashi, H., Yahata, N., Matsuura, M., Asai, K., Okubo, Y., et al. (2006). Language processing and human voice perception in schizophrenia: a functional magnetic resonance imaging study. *Biol. Psychiatry* 59, 948–957.

Koeda, M., Takahashi, H., Yahata, N., Matsuura, M., Asai, K., Okubo, Y., et al. (2007). Neural responses to human voice and hemisphere dominance for lexical-semantic processing–an fMRI study. *Methods Inf. Med.* 46, 247–250.

Kompus, K., Westerhausen, R., and Hugdahl, K. (2011). The "paradoxical" engagement of the primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies. *Neuropsychologia* 49, 3361–3369.

Kumari, V., Fannon, D., Ffytche, D. H., Raveendran, V., Antonova, E., Premkumar, P., et al. (2010). Functional MRI of verbal self-monitoring in schizophrenia: performance and illness-specific effects. *Schizophr. Bull.* 36, 740–755.

Leitman, D. I., Hoptman, M. J., Foxe, J. J., Saccente, E., Wylie, G. R., Nierenberg, J., et al. (2007). The neural substrates of impaired prosodic detection in schizophrenia and its sensorial antecedents. *Am. J. Psychiatry* 164, 474–482.

Leitman, D. I., Wolf, D. H., Laukka, P., Ragland, J. D., Valdez, J. N., Turetsky, B. I., et al. (2011). Not pitch perfect: sensory contributions to affective communication impairment in schizophrenia. *Biol. Psychiatry* 70, 611–618.

Mechelli, A., Allen, P., Amaro, E. Jr., Fu, C. H., Williams, S. C., Brammer, M. J., et al. (2007). Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Hum. Brain Mapp.* 28, 1213–1222.

Menon, V., Anagnoson, R. T., Mathalon, D. H., Glover, G. H., and Pfefferbaum, A. (2001). Functional neuroanatomy of auditory working memory in schizophrenia: relation to positive and negative symptoms. *Neuroimage* 13, 433–446.

Mitchell, R. L., Elliott, R., Barry, M., Cruttenden, A., and Woodruff, P. W. (2004). Neural response to emotional prosody in schizophrenia and in bipolar affective disorder. *Br. J. Psychiatry* 184, 223–230.

Mitchell, R. L., Elliott, R., and Woodruff, P. W. (2001). fMRI and cognitive dysfunction in schizophrenia. *Trends Cogn. Sci.* 5, 71–81.

Morrison, A. P., and Haddock, G. (1997). Cognitive factors in source monitoring and auditory hallucinations. *Psychol. Med.* 27, 669–679.

Ngan, E. T., Vouloumanos, A., Cairo, T. A., Laurens, K. R., Bates, A. T., Anderson, C. M., et al. (2003). Abnormal processing of speech during oddball target detection in schizophrenia. *Neuroimage* 20, 889–897.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.

Saarela, M. V., and Hari, R. (2008). Listening to humans walking together activates the social brain circuitry. *Soc. Neurosci.* 3, 401–409.

Scharpf, K. R., Wendt, J., Lotze, M., and Hamm, A. O. (2010). The brain's relevance detection network operates independently of stimulus modality. *Behav. Brain Res.* 210, 16–23.

Schettino, A., Lauro, L. R., Crippa, F., Anselmetti, S., Cavallaro, R., and Papagno, C. (2010). The comprehension of idiomatic expressions in schizophrenic patients. *Neuropsychologia* 48, 1032–1040.

Shamay-Tsoory, S. G., Tibi-Elhanany, Y., and Aharon-Peretz, J. (2006). The ventromedial prefrontal cortex is involved in understanding affective but not cognitive theory of mind stories. *Soc. Neurosci.* 1, 149–166.

Siegal, M., and Varley, R. (2002). Neural systems involved in "theory of mind". *Nat. Rev. Neurosci.* 3, 463–471.

Sommer, I. E., Ramsey, N. F., and Kahn, R. S. (2001). Language lateralization in schizophrenia, an fMRI study. *Schizophr. Res.* 52, 57–67.

Stein, J., and Richardson, A. (1999). Cognitive disorders: a question of misattribution. *Curr. Biol.* 9, R374–R376.

Tsukiura, T., and Cabeza, R. (2011). Remembering beauty: roles of orbitofrontal and hippocampal regions in successful memory encoding of attractive faces. *Neuroimage* 54, 653–660.

Uddin, L. Q., Kaplan, J. T., Molnar-Szakacs, I., Zaidel, E., and Iacoboni, M. (2005). Self-face recognition activates a frontoparietal "mirror" network in the right hemisphere: an event-related fMRI study. *Neuroimage* 25, 926–935.

Waters, F., Aleman, A., Fernyhough, C., and Allen, P. (2012). Report on the inaugural meeting of the International Consortium on Hallucination Research: a clinical and research update and 16 consensus-set goals for future research. *Schizophr. Bull.* 38, 258–262.

White, T. P., Francis, S. T., Joseph, V., O'Regan, E., Head, K. E., and Liddle, P. F. (2009). Evidence for reduced somatosensory lateralisation and focalisation in schizophrenia. *Psychiatry Res.* 174, 24–31.

Wible, C. G., Preus, A. P., and Hashimoto, R. (2009). A cognitive neuroscience view of schizophrenic symptoms: abnormal activation of a system for social perception and communication. *Brain Imaging Behav.* 3, 85–110.

Winston, J. S., O'Doherty, J., Kilner, J. M., Perrett, D. I., and Dolan, R. J. (2007). Brain systems for assessing facial attractiveness. *Neuropsychologia* 45, 195–206.

Woodruff, P. W., Wright, I. C., Bullmore, E. T., Brammer, M., Howard, R. J., Williams, S. C., et al. (1997). Auditory hallucinations and the temporal cortical response to speech in schizophrenia: a functional magnetic resonance imaging study. *Am. J. Psychiatry* 154, 1676–1682.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 18 February 2013; accepted: 08 May 2013; published online: 24 May 2013.

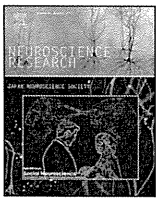
Citation: Koeda M, Takahashi H, Matsuura M, Asai K and Okubo Y (2013) Cerebral responses to vocal attractiveness and auditory hallucinations in schizophrenia: a functional MRI study. Front. Hum. Neurosci. 7:221. doi: 10.3389/fnhum.2013.00221

Neuroscience Research 90 (2015) 1–2

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures



Editorial

A critical evaluation of current social neuroscience knowledge and new directions in understanding social behavior

With advancements in non-invasive human neuroimaging techniques, such as fMRI, social neuroscience (i.e., the study of emotions and social cognition) has been gaining momentum since the late 1990s. In 2006, two journals, Social Neuroscience (http://www.psypress.com/journals/details/1747-0919/) and Social Cognitive and Affective Neuroscience (http://scan.oxfordjournals.org/), were founded. Both journals welcome animal and human research; they accept articles from broad fields of neuroscience, including neuroimaging, neuropsychology, pharmacology, genetics, neuroendocrinology and clinical studies. The research fields of empathy, social cognition, theory of mind, mirror neuron, self, morality, fairness/equality, and (social) decision-making have been widely investigated. However, given their interdisciplinary natures, there are some inconsistencies, miscommunications, and misinterpretations among the fields. In this issue, four review articles critically reviewed the current knowledge of empathy (Lamm and Majdandžić, 2014), self-face recognition (Sugiura, 2014), fairness (Aoki et al., 2014), reward and decision-making (Wiehler and Peters, 2014). Four additional review articles focused on new directions in social neuroscience. Koike et al. (2014) reviewed a hyper-scanning technique to simultaneously record brain activity from two subjects, and Kasai et al. (2014) emphasized the necessity of two-subject imaging for understanding brain dynamics during natural social situations. Tsuda et al. (2014) reviewed the emerging field of neural information science for communication, and Asada (2014) proposed a new approach for cognitive developmental robotics to model artificial empathy.

This field represents a relatively young area, but social neuroscience is never unrelated to traditional behavioral and neuroscientific topics. Four research reports using relatively traditional approaches appear in this special issue. Using tool-use tasks, Wakusawa et al. (2014) reported the neural correlates of adaptive ability in novel situations, which are required in social situations. Okada et al. (2014) reported that deaf individuals recruited the left superior temporal gyrus when memorizing finger alphabets, suggesting that deaf individuals utilized phonological representation. Matsumoto et al. (2014) demonstrated that eye movement during biological motion perception is associated with the capacity for empathy in schizophrenic patients. Hattori et al. (2014) reported that oxytocin receptor-null mice showed equal levels of territorial aggressive behavior toward their own strain, as well as different strains, indicating interstrain social recognition impairment.

We have organized Japanese social neuroscience meetings over the past 5 years, with the aim of facilitating interdisciplinary corroborations and encouraging young researchers and students to participate in the field. The Ministry of Education, Culture, Sports, Science and Technology of Japan is funding some interdisciplinary Grants-in-Aid for Scientific Research in Innovative Areas, such as prediction and decision-making, neural information science for communication, adolescent mind and self-regulation, empathic systems, science of mental time, face perception and recognition, etc. These projects are related to social neuroscience, a field in which many contributors to this issue are involved. These projects have also been encouraging young researchers to gain knowledge and skills from specialists in fields other than their own. Innovative technical advancements are being rapidly achieved. We hope that young researchers will utilize innovative methods to help mature the field of social neuroscience.

References

Aoki, R., Yomogida, Y., Matsumoto, K., 2014. The neural bases for valuing social equality. Neurosci. Res.

Asada, M., 2014. Development of artificial empathy. Neurosci. Res.

Okada, R., Nakagawa, J., Takahashi, M., Kanaka, N., Fukamauchi, F., Watanabe, K., Namatame, M., 2014. The deaf utilize phonological representations in visually presented verbal memory tasks. Neurosci. Res.

Hattori, T., Kanno, K., Nagasawa, M., Nishimori, K., Mogi, K., Kikusui, T., 2014. Impairment of interstrain social recognition during territorial aggressive behavior in oxytocin receptor-null mice. Neurosci. Res.

Kasai, K., Fukuda, M., Yahata, N., Morita, K., Fujii, N., 2014. The future of real-world neuroscience: imaging techniques to assess active brains in social environments. Neurosci. Res.

Koike, T., Tanabe, H., Sadato, N., 2014. Hyperscanning neuroimaging technique to reveal the two-in-one system in social interactions. Neurosci. Res.

Lamm, C., Majdandžić, J., 2014. The role of shared neural activations, mirror neurons, and morality in empathy – a critical comment. Neurosci. Res.

Matsumoto, Y., Takahashi, H., Murai, T., Takahashi, H., 2014. Visual processing and social cognition in schizophrenia: relationships among eye movements, biological motion perception, and empathy. Neurosci. Res.

Sugiura, M., 2014. Three faces of self-face recognition: potential for a multi-dimensional diagnostic tool. Neurosci. Res.

Tsuda, I., Yamaguchi, Y., Hashimoto, T., Okuda, J., Kawasaki, M., Nagasawa, Y., 2014. Study of the neural dynamics for understanding communication in terms of complex hetero systems. Neurosci. Res.

Wakusawa, K., Sugiura, M., Sassa, Y., Jeong, H., Yomogida, Y., Horie, K., Sato, S., Yokoyama, H., Kure, S., Takei, N., Mori, N., Kawashima, R., 2014. Adaptive ability to cope with atypical or novel situations involving tool use: an fMRI approach. Neurosci. Res.

http://dx.doi.org/10.1016/j.neures.2014.12.008

Wiehler, A., Peters, J., 2014. Reward-based decision making in pathological gambling: the roles of risk and delay. Neurosci. Res.

Hidehiko Takahashi*
Department of Psychiatry, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawara-cho, Sakyo-ku, Kyoto 606-8507, Japan

Tetsuya Matsuda[1]
Brain Science Institute, Tamagawa University, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan

* Corresponding author. Tel.: +81 75 751 3386; fax: +81 75 751 3246.
E-mail addresses: hidehiko@kuhp.kyoto-u.ac.jp (H. Takahashi), tetsuya@lab.tamagawa.ac.jp (T. Matsuda).

[1] Tel.: +81 42 739 8265; fax: +81 42 739 8265.

Neuroscience Research 90 (2015) 83–89

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

The deaf utilize phonological representations in visually presented verbal memory tasks

Rieko Okada[a], Jun Nakagawa[a,b], Muneyoshi Takahashi[a], Noriko Kanaka[a], Fumihiko Fukamauchi[c,d], Katsumi Watanabe[e], Miki Namatame[c], Tetsuya Matsuda[a,*]

[a] Tamagawa University Brain Science Institute, 6-1-1 Tamagawa Gakuen, Machida City, Tokyo 194-8610, Japan
[b] Section of Liaison Psychiatry & Palliative Medicine, Graduate School of Tokyo Medical & Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan
[c] Faculty of Industrial Technology, National University Corporation Tsukuba University of Technology, 4-12-7 Kasuga, Tsukuba City, Ibaraki 305-8521, Japan
[d] Enomoto Clinic, 1-2-5 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-0021, Japan
[e] Research Center for Advanced Science and Technology, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan

ARTICLE INFO

Article history:
Received 27 September 2014
Received in revised form 27 October 2014
Accepted 10 November 2014
Available online 10 December 2014

Keywords:
Deaf
Phonological representation
Visual processing
Hearing

ABSTRACT

The phonological abilities of congenitally deaf individuals are inferior to those of people who can hear. However, deaf individuals can acquire spoken languages by utilizing orthography and lip-reading. The present study used functional magnetic resonance imaging (fMRI) to show that deaf individuals utilize phonological representations via a mnemonic process. We compared the brain activation of deaf and hearing participants while they memorized serially visually presented Japanese *kana* letters (Kana), finger alphabets (Finger), and Arabic letters (Arabic). Hearing participants did not know which finger alphabets corresponded to which language sounds, whereas deaf participants did. All of the participants understood the correspondence between Kana and their language sounds. None of the participants knew the correspondence between Arabic and their language sounds, so this condition was used as a baseline. We found that the left superior temporal gyrus (STG) was activated by phonological representations in the deaf group when memorizing both Kana and Finger. Additionaly, the brain areas associated with phonological representations for Finger in the deaf group were the same as the areas for Kana in the hearing group. Overall, despite the fact that they are superior in visual information processing, deaf individuals utilize phonological rather than visual representations in visually presented verbal memory.

1. Introduction

Individuals who are congenitally deaf do not acquire spoken languages in the same way as hearing individuals. It has been shown that deaf individuals acquire spoken languages using methods that are different from hearing individuals, such as by orthography or lip-reading (Aparicio et al., 2007; Beal-Alvarez et al., 2012). However, other studies provided evidence that it is difficult for deaf individuals to acquire phonological units. They have also been shown to be inferior in their phonological abilities compared to hearing individuals (Dodd, 1979; Leybaert and Alegria, 1995; Montgomery et al., 1987).

The term "phonological unit" refers to sound information that functions in a particular language, and a phonological representation is a mental representation of the information of the sounds in the brain. Concretely, sound information that comprises words and sentences is represented in the brain when listening to words and sentences. Phonological representations reportedly occur not only when one listens to words/sentences, but also when reading them (Aparicio et al., 2007; Baddeley et al., 1981).

A number of behavioral experiments have shown that phonological representations play an important role in facilitating language processing and memorization. For instance, it has long been reported that phonological representations contribute to verbal short-term memory (Baddeley, 1986; Burgess and Hitch, 1996), especially the memory of the order of serially presented words (Nairne and Kelley, 2004; Watkins et al., 1974; Wickelgren, 1965). According to these studies, when one recalls serially presented

---

Abbreviations: STG, superior temporal gyrus; MTG, middle temporal gyrus; SPM, Statistical Parametric Mapping; EPI, echo planar imaging; MNI, Montreal Neurological Institute; BA, Brodmann area; MOG, middle occipital gyrus; MFG, middle frontal gyrus.

[*] Corresponding author. Tel.: +81 42739 8265; fax: +81 42739 8265.
E-mail address: tetsuya@lab.tamagawa.ac.jp (T. Matsuda).

http://dx.doi.org/10.1016/j.neures.2014.11.004
0168-0102/© 2014 Published by Elsevier Ireland Ltd.