

Functional MRI of Verbal Self-monitoring in Schizophrenia: Performance and Illness-Specific Effects

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Previous small-sample studies have shown altered frontotemporal activity in schizophrenia patients with auditory hallucinations and impaired monitoring of self-generated speech. We examined a large cohort of patients with schizophrenia ($n = 63$) and a representative group of healthy controls ($n = 20$) to disentangle performance, illness, and symptom-related effects in functional magnetic resonance imaging-detected brain abnormalities during monitoring of self- and externally generated speech in schizophrenia. Our results revealed activation of the thalamus (medial geniculate nucleus, MGN) and frontotemporal regions with accurate monitoring across all participants. Less activation of the thalamus (MGN, pulvinar) and superior-middle temporal and inferior frontal gyri occurred in poorly performing patients (1 standard deviation below controls' mean; $n = 36$), relative to the combined group of controls and well-performing patients. In patients, (1) greater deactivation of the ventral striatum and hypothalamus to own voice, combined with nonsignificant activation of the same regions to others' voice, associated positively with negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive social avoidance) regardless of performance and (2) exaggerated activation of the right superior-middle temporal gyrus during undistorted, relative to distorted, feedback associated with both positive symptoms (hallucinations, persecution) and poor performance. A further thalamic abnormality

characterized schizophrenia patients regardless of performance and symptoms. We conclude that hypoactivation of a neural network comprised of the thalamus and frontotemporal regions underlies impaired speech monitoring in schizophrenia. Positive symptoms and poor monitoring share a common activation abnormality in the right superior temporal gyrus during processing of degraded speech. Altered striatal and hypothalamic modulation to own and others' voice characterizes emotionally withdrawn and socially avoidant patients.

Key words: psychosis/self/others/social avoidance/fMRI/frontal/temporal/thalamus

Introduction

According to Kircher and David,¹ self-consciousness consists of (a) self-agency, the sense of authorship of one's actions, (b) self-coherence, the sense of being a bounded physical whole, (c) self-affectivity, experiencing affect in relation to other experiences of self, and (d) self-history, the sense of one's temporal continuity. Self-monitoring, the cognitive ability distinguishing the products of self-generated actions or thoughts from those of other-generated actions or thoughts, contributes to the sense of self-agency.² Some of the core symptoms of schizophrenia are thought to stem from impaired self-monitoring.³ Empirical investigations of patients with schizophrenia have shown deficient self-monitoring in the visual,^{4–7} tactile,⁸ and verbal domains.^{9–13}

The temporal and frontal lobes are implicated in successful self-monitoring.¹³ A few published studies addressing the functional neuroanatomy of verbal self-monitoring in schizophrenia have shown reduced superior-middle temporal lobe (TL) activity during verbal imagery in patients with auditory hallucinations (AH)^{14–16} and reduced left but increased right TL activation to external speech in association with hallucinatory behavior.¹⁷ More recently, functional magnetic resonance imaging (fMRI) studies have revealed reduced connectivity between the left superior temporal gyrus (STG) and anterior cingulate (AC) during the appraisal of own speech in patients with AH ($n = 10$) compared with healthy

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controls (HC; $n = 10$)¹⁸ and altered activation in the left STG and AC during misattribution of self-generated speech in patients with AH ($n = 11$) compared with those without AH ($n = 10$) and HC ($n = 10$).¹⁹ The patients showing activation abnormalities in these studies were also, on average, impaired in judging self-generated speech.

The present study aimed to disentangle performance, illness, and symptom-related effects in fMRI-detected brain abnormalities during monitoring of self- and externally generated speech in schizophrenia using a large group of patients and a representative group of HC employing an established fMRI-compatible task.²⁰ We hypothesized that (1) patients will show deficient performance compared with HC and (2) there will be decreased frontotemporal activation in patients performing in the “deficient” range. We further examined illness process-related (present across the patient group regardless of performance or symptoms) and symptoms-related (associated with symptoms but unrelated to performance) abnormalities. Based on previous evidence,¹³ we anticipated an association between STG dysfunction and positive symptoms, especially hallucinations. Although there is evidence for a positive association between negative symptoms and error-correcting ability in a self-monitoring paradigm,²¹ no previous study has examined the relationship between negative symptoms and fMRI-detected brain activity during monitoring of self- and externally generated speech in schizophrenia. This part of our investigation was exploratory.

Methods

Participants and Design

Seventy right-handed²² outpatients with schizophrenia, of whom 63 provided usable data. All patients were in a chronic illness phase and on stable doses of antipsychotics for at least 3 months. Twenty right-handed HC matched, on average, on age and sex to the patient group were also studied (see table 1 for participants' characteristics). All participants had intact hearing.

The study had local ethics committee approval. All participants provided written informed consent.

Assessments

The diagnosis²³ in patients was confirmed, and symptoms were rated using the Positive and Negative Syndrome Scale (PANSS)²⁴ by a trained psychiatrist. The absence of a clinical diagnosis²⁵ in HC was also confirmed. The current IQ²⁶ was measured in all participants.

fMRI Paradigm and Procedure

All participants performed a self-monitoring task while undergoing fMRI. Participants were presented with single words on a computer screen (visible for 750 ms, inter-stimulus interval 16.25 s), viewed via a prismatic mirror fitted in the radiofrequency head coil, as they lay in the

Table 1. Demographic and Clinical Characteristics of Study Participants

	Healthy Participants ($n = 20$, 70% Men)	Patients ($n = 63$, 74.6% Men)
Demographics	Mean (SD)	Mean (SD)
Age (y) ^a	33.95 (10.37)	37.95 (9.63)
Education (y) ^b	15.70 (2.73)	13.79 (2.57)
Current IQ ^c	122.15 (12.06)	103.98 (20.44)
Clinical Characteristics (Patients Only)	Range	Mean (SD)
Age at illness onset (y)	10–50	24.71 (7.97)
Duration of illness	1–43	13.24 (9.51)
PANSS: positive symptoms ^d	7–25	16.17 (4.81)
PANSS: negative symptoms	7–27	17.40 (4.77)
PANSS: general psychopathology	18–56	30.51 (6.75)
Total PANSS score	37–108	65.78 (13.81)
Medication		Forty-eight patients (75%) on atypical and 10 (17.2%) on typical antipsychotics. Remaining 5 patients on both atypical and typical antipsychotics.

^a t ($df = 81$) = 1.59, $P > .10$.

^b t ($df = 81$) = 2.84, $P = .01$.

^c t ($df = 80$) = 2.99, $P = .004$ (IQ not assessed in one patient, n reduced to 62).

^dPANSS = Positive and Negative Syndrome Scale.²⁴

scanner, and were instructed to read each word aloud. The participant's speech was transformed through a software program and a DSP.FX digital effects processor (Power Technology, Brisbane, CA), amplified by a computer sound card, and relayed back through an acoustic MRI sound system (Ward Ray-Premis, Hampton Court, UK) and pneumatic tubes within the ear protectors at a volume of 91 dB (SD 2). The volume of the feedback was sufficient to overcome the bone conduction of the participant's own voice. The verbal feedback was (a) their own voice (self-undistorted), (b) their own voice lowered in pitch by 4 semitones (self-distorted), (c) voice of another person matched on participant's sex (other-undistorted), or (d) another person's voice with the pitch lowered by 4 semitones (other-distorted). The level of pitch distortion was determined based on findings from previous neuroimaging studies of verbal self-monitoring.^{20,27} Participants registered their responses regarding the origin of feedback by using the button box with the “self” button press for their voice, the “other” button press for “other” voice, or the “unsure” button if they were unsure about the nature of the feedback.

Words “self,” “other,” and “unsure” were displayed on the screen and were outlined in black after each participant’s response. Accuracy of the responses was recorded online. Participants’ occasional failures to press a button were recorded as nonresponses. In total, 64 words were presented during the experiment. Each condition occurred 16 times in a pseudorandom order. Participants were familiarized with the experimental procedures prior to scanning.

Image Acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Signa system (General Electric, Milwaukee, WI). A quadrature birdcage head coil was used for radio frequency transmission and reception. In each of 14 near-axial noncontiguous planes (slice thickness = 7.0 mm, interslice gap = 1 mm) parallel to the intercommissural (ac-pc) plane, T2*-weighted MR images depicting blood oxygenation level-dependent (BOLD) contrast were acquired over 1.1 seconds using a “clustered” acquisition (12–14) (echo time = 40 ms, 70° flip angle), which created a relative silent period of 2.15 seconds for each stimulus within a repetition time of 3.25 seconds and the interstimulus interval of 16.25 seconds, yielding 5 brain volumes for each trial. A clustered acquisition sequence was used to minimize artifacts associated with overt speech during image acquisition.²⁰

Data Analysis

Demographic and Behavioral Measures. Patients and HC were compared on demographic characteristics using independent sample *t* tests. Group differences in performance (the percentage of correct, incorrect, or unsure responses as well as non-responses) were examined by group (patients, HC) × source (self, other) × distortion (undistorted, distorted) analysis of variance (ANOVA) with group as a between-subjects factor and source and distortion as within-subjects factors, followed by post hoc analyses as appropriate. Sex as a between-subjects factor showed no main or interactive effects in performance and was subsequently removed. Effect sizes for group differences in performance are reported as partial η^2 (the proportion of variance associated with a factor).

The associations between performance variables differentiating patients from HC and PANSS scores (subscale and total) were examined using Pearson correlations.

All analyses were carried out using SPSS 15. Alpha level for testing significance of effects was $P = .05$, 2 tailed, unless stated otherwise.

Functional Magnetic Resonance Imaging

Preprocessing. For each participant, the volume functional time series were motion corrected, transformed

into stereotactic space, spatially smoothed with a 10-mm full-width at half-maximum Gaussian filter and band pass filtered using statistical parametric mapping software (SPM2; <http://www.fil.ion.ucl.ac.uk/spm2>).

Creation of Patient Subgroups

The patient sample was divided, on the basis of their total percentage of correct answers (accuracy rates for the 4 conditions were highly positively correlated), into 2 groups: good and poor performers. The mean percentage of total correct answers in HC minus 1 SD (mean = 78.91, SD = 11.00) was used to define a deficit cutoff score of 67.91 ($\leq 67.91\%$ = deficient performance).

Models and Inferences

We focused on brain activity during trials with correct answers. There were too few errors for the self-undistorted condition in the majority of HC and patients classified as good performers to allow the analysis of brain responses during errors.

fMRI data were analyzed using a 2-stage random-effect procedure.²⁸ The first stage identified subject-specific activations. Although there were relatively fewer correct trials per participant in the poor performance group, this group had sufficient (and the largest) number of participants to allow ample power in further analysis steps. We then identified task-related activations (threshold $P < .05$ corrected for multiple comparisons at cluster level) using 1-sample *t* tests across all participants. The second stage of analysis involved separate ANOVAs within SPM for each task condition and then at the levels of source (self-undistorted + self-distorted vs other undistorted + other distorted) and distortion (self-undistorted + other-undistorted vs self-distorted + other-distorted) to identify regions of activity ($P = .05$ corrected for multiple comparisons at cluster level) differentiating (a) good (HC + patients) from poor performers (patients only) and (b) patients (regardless of performance) from HC.

Next, subject-specific activation values were extracted from voxels showing the maximum group difference in each cluster and explored for possible relationships with performance and symptom scores (within SPSS). The associations with performance and PANSS subscale and total scores were examined using Pearson correlations and with individual PANSS item scores (if detected at the total or subscale level) using Spearman rank-order correlations.

Results

Participant Characteristics

HC and patients were comparable on age and sex distribution, but patients had significantly fewer years of education and lower IQ (table 1).

Table 2. Verbal Monitoring Performance in Patients and Healthy Participants and the Results of the Analysis of Simple Main Effects for Variables Showing Significant Main or Interactive Effects Involving the Group Factor

Condition	Healthy Participants (<i>n</i> = 20) Mean (SD)	Patients (<i>n</i> = 63), Mean (SD)	<i>P</i> Value (Statistic)	Effect Size (Partial η^2)
% Correct				
Self-undistorted	92.81 (6.17)	82.94 (19.64)	.03 ($F_{1,81} = 4.87$)	0.057
Self-distorted	75.31 (28.49)	50.19 (36.49)	.006 ($F_{1,81} = 7.91$)	0.089
Other-undistorted	85.31 (20.00)	61.01 (31.88)	.002 ($F_{1,81} = 10.28$)	0.113
Other-distorted	62.19 (25.44)	54.26 (35.35)	ns ($F_{1,81} = 0.86$)	
Total	78.91 (11.00)	62.11 (15.79)	<.001 ($F_{1,81} = 19.51$)	0.194
% Incorrect				
Self-undistorted	1.87 (4.58)	3.37 (6.43)	ns ($F_{1,81} = 0.93$)	
Self-distorted	16.25 (22.43)	33.93 (33.63)	.03 ($F_{1,81} = 4.82$)	0.056
Other-undistorted	10.62 (14.06)	27.18 (29.12)	.017 ($F_{1,81} = 5.98$)	0.069
Other-distorted	20.93 (22.15)	29.36 (32.49)	ns ($F_{1,81} = 1.17$)	
Total	12.42 (7.27)	23.47 (12.41)	<.001 ($F_{1,81} = 14.24$)	0.149
% Unsure				
Self-undistorted	0.31 (1.40)	5.26 (12.91)		
Self-distorted	6.87 (15.16)	12.80 (17.00)		
Other-undistorted	3.75 (9.80)	9.23 (12.34)		
Other-distorted	15.00 (21.11)	13.79 (20.05)		
Total	6.48 (8.62)	10.26 (12.08)		
% Nonresponses				
Self-undistorted	5.00 (3.85)	8.43 (9.99)		
Self-distorted	1.56 (4.91)	3.07 (5.60)		
Other-undistorted	0.31 (1.39)	2.48 (7.06)		
Other-distorted	1.87 (3.57)	2.58 (7.15)		
Total	2.19 (2.45)	4.14 (5.24)		

Performance

Years in education was not associated with performance when examined separately in HC and patients or across the entire sample (P 's > .15). IQ showed modestly positive correlations with percentage of correct answers during the other-distorted condition ($r_{20} = 0.530$, $P = .016$) but not during the other 3 conditions (self-undistorted $r = 0.360$, self-distorted $r = 0.129$, other-undistorted $r = 0.10$; P 's > .10) in controls and during the self-undistorted ($r_{62} = 0.474$, $P = .016$) and other-distorted ($r = 0.503$, $P = .001$) but not (P 's > .10) during the self-undistorted ($r = 0.205$) or other-undistorted ($r = 0.197$) conditions in patients.

HC showed more accurate performance than patients ($F_{1,81} = 19.52$, $P = .001$, $\eta^2 = 0.194$). Both groups had more accurate performance during the undistorted than the distorted conditions ($F_{1,81} = 76.33$; $P < .001$, $\eta^2 = 0.485$). A group \times source \times distortion interaction was present ($F_{1,81} = 4.33$, $P = .04$, $\eta^2 = 0.051$), with HC performing significantly better than patients during the self-undistorted, self-distorted, and other-undistorted conditions but not during the other-distorted condition, possibly due to a much reduced accuracy in this condition in HC (table 2).

Complementing the results for percentage of correct answers, patients made more misattributions than HC ($F_{1,81} = 14.26$, $P < .001$, $\eta^2 = 0.150$). This effect was significantly present only for the self-distorted and other-

undistorted conditions (table 2), although the group \times source \times distortion interaction fell short of formal significance ($F_{1,81} = 3.78$, $P = .06$, $\eta^2 = 0.045$). Both groups made more errors during the distorted than the undistorted conditions ($F_{1,81} = 46.21$, $P < .001$, $\eta^2 = 0.363$), especially during the other-distorted condition (source \times distortion: $F_{1,81} = 6.72$, $P = .01$, $\eta^2 = 0.08$).

The patients and HC were not significantly different for the percentage of unsure responses ($F < 2.40$ for group and group \times source \times distortion). Both groups made more unsure responses during the distorted, relative to undistorted ($F_{1,81} = 14.40$, $P < .001$, $\eta^2 = 0.15$), and during the other, relative to self, conditions ($F_{1,81} = 9.60$, $P = .003$, $\eta^2 = 0.11$).

No significant effects involving the group were detected for the percentage of nonresponses ($F < 2.15$ for group and group \times source \times distortion).

Across the entire patient sample, no significant or consistent relationships were found between PANSS total or subscale scores and performance accuracy (r range: -0.20 to $+0.28$) or error rate (r range: -0.22 to $+0.17$).

Good and Poor Performance Patients

Twenty-seven patients met the criterion for good and 36 for poor performance. Of 27 patients classified as good performers, 4 patients were excluded due to an odd performance pattern: 3 patients did not make any correct responses during the self-distorted condition

Table 3. Performance and Demographic and Clinical Characteristics of Good and Poor Performance Patient Groups

Performance	Good Performance Patients ($n = 23$, 78.3% Men), Mean (SD)	Poor Performance Patients ($n = 36$, 69.4% Men), Mean (SD)
% Correct		
Self-undistorted	93.21 (5.93)	75.52 (22.97)
Self-distorted	67.12 (29.99)	42.53 (35.91)
Other-undistorted	79.35 (15.47)	45.49 (32.34)
Other-distorted	64.67 (24.69)	45.65 (38.08)
Total	76.09 (7.24)	52.32 (2.21)
Demographic and clinical characteristics		
Age (y)	35.57 (9.61)	40.08 (9.47)
Education (y)	14.21 (2.83)	13.67 (2.51)
Current IQ	101.26 (21.06)	101.43 (20.84)
Age at illness onset (y)	23.78 (8.08)	25.22 (8.22)
Duration of illness	11.78 (8.92)	14.86 (9.95)
PANSS: positive symptoms	17.30 (4.60)	15.64 (4.92)
PANSS: negative symptoms	17.09 (4.76)	17.89 (4.97)
PANSS: general psychopathology	32.35 (6.81)	32.66 (6.82)
Total PANSS score	66.74 (14.33)	66.19 (13.85)
Medication	Twenty patients on atypical, 2 on typical, and 1 on both atypical and typical antipsychotics.	Twenty-six patients on atypical, 7 on typical, and 3 on both atypical and typical antipsychotics.

Note: PANSS = Positive and Negative Syndrome Scale.²⁴

and 1 patient made no correct response during the other-distorted condition despite excellent performance during the remaining 3 conditions.

As expected, patients classified as good performers had better performance than poorly performing patients (P 's $< .05$), but no clinical or demographic characteristics differentiated the 2 groups (P 's $> .05$) (table 3).

Functional Magnetic Resonance Imaging

Task-Related Activation Patterns Across All Participants.

Individual Conditions. A network of regions involving (bilaterally) the thalamus (medial geniculate nucleus, MGN), superior-middle TL, inferior frontal gyrus (IFG), insula, and putamen were activated in all conditions, across all participants (table 4, figure 1). The lingual gyrus (mainly right-sided) was activated during the self conditions.

The parahippocampal gyrus, posterior cingulate (PC), and medial frontal gyrus (MFG)/AC were deactivated during all conditions. The caudate nucleus was deactivated during the 2 self conditions and the angular gyrus during the 2 other conditions.

Source and Distortion. The angular gyrus, extending to the PC, showed differential activity in the other $<$ self-contrast; this effect was due to stronger deactivation of

these areas during the other, compared with self, conditions regardless of distortion (table 5, figure 1). The caudate activity also differentiated the self and other conditions (regardless of distortion) (see further, diagnosis and symptom effects in this area). A cluster located in the right transverse temporal gyrus, extending to the right IFG, showed greater activity during the undistorted, compared with distorted, feedback conditions (see further, diagnosis and performance effects). A small cluster in the AC showed greater activity during the distorted, relative to undistorted, conditions, but this effect failed to reach corrected significance.

Good Performers Vs Poor Performers

Good performers showed greater activity bilaterally in the superior-middle TL during all conditions than poor performers (table 6, figure 2). They also showed greater thalamic and putamen activity during all, except other-undistorted, conditions, and in the IFG and middle occipital gyrus during the self-undistorted condition.

Poor performers showed more activity than good performers in the medial prefrontal and posterior temporal parietal cortices during all conditions (failed to reach corrected significance in the self-distorted condition, thus not presented in table or figure). These differences occurred due to stronger deactivation of these areas (figure 1) in good, relative to poor, performers.

Poor and good performers were also differentiated by right IFG activity. Good, but not poor, performers showed more activity in these regions during the self, compared with other, conditions (regardless of distortion).

Patients Vs Healthy Participants

Patients, regardless of performance, showed less activity than HC in the thalamus (pulvinar) during the self-undistorted condition. They showed more activity bilaterally in the STG during the self-undistorted condition and in the left STG during the other-distorted condition. Subject-specific activation values in these regions did not correlate with age, age at illness onset, illness duration, PANSS scores, IQ, or performance in patients.

Patients showed more activity than HC in the ventral striatum, hypothalamus, and part of the thalamus in the other $>$ self-contrast (table 7, figure 3, source \times group). This effect occurred due to greater deactivation of these regions to own voice (note that the caudate showed deactivation during the self-conditions across the whole sample due to this effect mainly in patients, figure 1), combined with nonsignificant activation of the same regions to someone else's voice (not shown) and associated positively with negative symptoms. Within the patient group, greater ventral striatal-hypothalamic activity during other $>$ self-contrast (figure 3, source \times group) correlated with higher negative symptoms score ($r = 0.293$, $P = .05$). At the individual symptom level, blunted affect ($\rho = 0.369$, $P = .01$), emotional withdrawal ($\rho = 0.332$, $P = .026$),

Table 4. Brain Areas Showing Significant Activation Increases and Decrease in Association With Individual Task Conditions (Voxel Threshold $P = .005$)

4a. Increases								
Cluster Size (Voxels n)	Brain Region	Brodmann Area (BA)	Side	MNI Coordinates			Voxel T Value	Cluster P (Corrected for Multiple Comparisons)
				x	y	z		
20225	Self-undistorted			x	y	z		
	Superior temporal gyrus (extends bilaterally to the inferior frontal gyrus, insula, putamen, and thalamus)	22	R	56	-24	4	14.33	<.001
		22	L	-50	-36	16	14.25	
	22	R	56	-34	16	11.21		
2181	Lingual gyrus/cuneus	18	R	18	-66	6	6.32	<.001
		18	L	-14	-76	12	5.84	
		18	L	-18	-78	22	4.85	
7212	Self-distorted							
	Superior temporal gyrus (extends to the inferior frontal gyrus, insula, putamen, and thalamus)	22	R	58	-26	4	13.44	<.001
		22	R	58	-36	14	11.42	
	Postcentral gyrus	40	R	60	-22	20	10.59	
9231	Heschl's gyrus (extends to the inferior frontal gyrus, insula, putamen, and thalamus)	41	L	-54	-36	14	11.91	<.001
	Superior temporal gyrus	22	L	-58	-24	4	9.85	
	Thalamus	n/a	R	10	-16	4	9.65	
1305	Cuneus	19	L	-20	-80	34	7.50	.002
		18	L	-14	-76	12	5.06	
2226	Middle occipital gyrus	19	R	30	-78	26	5.43	<.001
		19	R	16	-78	26	5.36	
		19	R	44	-70	2	4.76	
7258	Other-undistorted							
	Superior temporal gyrus (extends to the inferior frontal gyrus, insula, and putamen)	22	R	56	-26	0	12.56	<.001
		22	R	62	-36	8	10.78	
	22	R	46	-30	14	9.43		
7066	(extends anteriorly to the Broca's area and posteriorly to Wernicke's area, insula, and putamen)	22	L	-54	-38	14	11.53	<.001
		44	L	-34	22	8	7.91	
		22	L	-58	2	-2	5.80	
2296	Brain stem	n/a	L	-2	-30	-8	7.34	<.001
	Thalamus	n/a	R	12	-16	8	6.68	
	Thalamus	n/a	L	-6	-20	4	5.45	
9567	Other-distorted							
	Superior temporal gyrus (extends anteriorly to the Broca's area and posteriorly to Wernicke's area)	22	L	-52	-32	10	10.71	<.001
	Thalamus	n/a	R	10	-18	4	10.58	
	22	L	-56	-12	12	10.48		
5945	Superior temporal gyrus (extends anteriorly to the inferior frontal gyrus and insula)	22	R	62	-16	4	10.51	<.001
		22	R	64	-36	14	9.05	
	Precentral gyrus	6	R	60	-4	12	8.08	

Table 4. Continued

4b. Decreases								
Cluster Size (Voxels <i>n</i>)	Brain Region	Brodmann Area (BA)	Side	MNI Coordinates			Voxel <i>T</i> Value	Cluster <i>P</i> (Corrected for Multiple Comparisons)
4241	Self-undistorted							
	Posterior cingulate gyrus	30	L	-22	-36	16	10.32	<.001
		30	R	22	-40	12	9.76	
Parahippocampal gyrus	n/a	R	32	-46	2	9.28		
4587	Medial frontal gyrus	32	R	6	32	-4	8.66	<.001
	Anterior cingulate gyrus	24	R	6	24	0	8.42	
	Caudate nucleus	n/a	R	4	14	6	8.12	
5701	Self-distorted							
	Parahippocampal gyrus	n/a	L	-32	-50	0	9.04	<.001
	Calcarine sulcus	n/a	L	-26	-46	10	8.65	
Parahippocampal gyrus	n/a	R	32	-44	6	8.62		
3639	Caudate nucleus	n/a	L	-2	18	4	7.16	<.001
	Anterior cingulate gyrus	24	L	-16	28	2	7.02	
		24	R	10	26	2	6.65	
5364	Other-undistorted							
	Parahippocampal gyrus	n/a	L	-30	-48	4	10.72	<.001
	Angular gyrus	39	L	-46	-66	28	9.62	
Posterior cingulate gyrus	30	R	32	-44	16	8.30		
2532	Anterior cingulate gyrus	24/32	L	-2	34	2	7.75	<.001
	(extending to medial frontal gyrus)	32	R	20	32	-4	6.67	
		32	R	10	38	-2	6.53	
4032	Other-distorted							
	Posterior cingulate gyrus	30	R	22	-52	18	7.02	<.001
		23	L	16	-50	26	7.00	
Angular gyrus	39	R	34	-50	16	6.76		
3645	Anterior cingulate gyrus	24	L	-8	26	10	5.94	<.001
	Medial frontal gyrus	10	L	-12	46	-8	5.51	
		10/32	L	-22	42	0	5.41	

Note: MNI = Montreal Neurological Institute; n/a = not applicable.

poor rapport ($\rho = 0.359$, $P = .015$), and passive social avoidance ($\rho = 0.335$, $P = .025$) contributed to this relationship; poor abstract thinking, lack of spontaneity, and stereotyped thinking items were uncorrelated ($P > .15$).

Patients also showed greater activity in the right TL extending to the right IFG and parietal regions during conditions with undistorted, relative to distorted, feedback (regardless of source); HC showed the opposite pattern although to a lesser degree. This activity change in patients did not correlate with IQ ($r = -0.134$) but correlated negatively with performance (percentage of total correct $r = -0.364$, $P = .014$) and positively with positive symptoms ($r = 0.349$, $P = .019$), specifically with hallucinations ($\rho = 0.437$, $P = .003$), persecution ($\rho = 0.320$, $P = .032$), and disorganization ($\rho = 0.320$, $P = .032$).

Discussion

We studied a large number of patients and a representative group of HC using fMRI and an established fMRI-

compatible task with the main objective of disentangling performance, illness, and symptom-related effects in fMRI-detected brain abnormalities during self- and externally generated speech monitoring in schizophrenia.

Behavioral Findings: Impaired Performance in Patients

The data confirm our hypothesis of impaired performance in patients, relative to HC. This deficit, however, was not limited to misattribution of "self-generated" voice (externalizing bias) because the patients also misattributed another person's voice to themselves (internalizing bias). While it is possible that a subgroup of patients show only externalizing bias, studies using similar paradigms to those used in the present study point to a more general monitoring deficit affecting judgments of both self-generated and another person's voice in schizophrenia.^{11,29} A possible reason for this might be that participants can perceive their own voice while reading the words across all conditions,^{30,31} meaning all

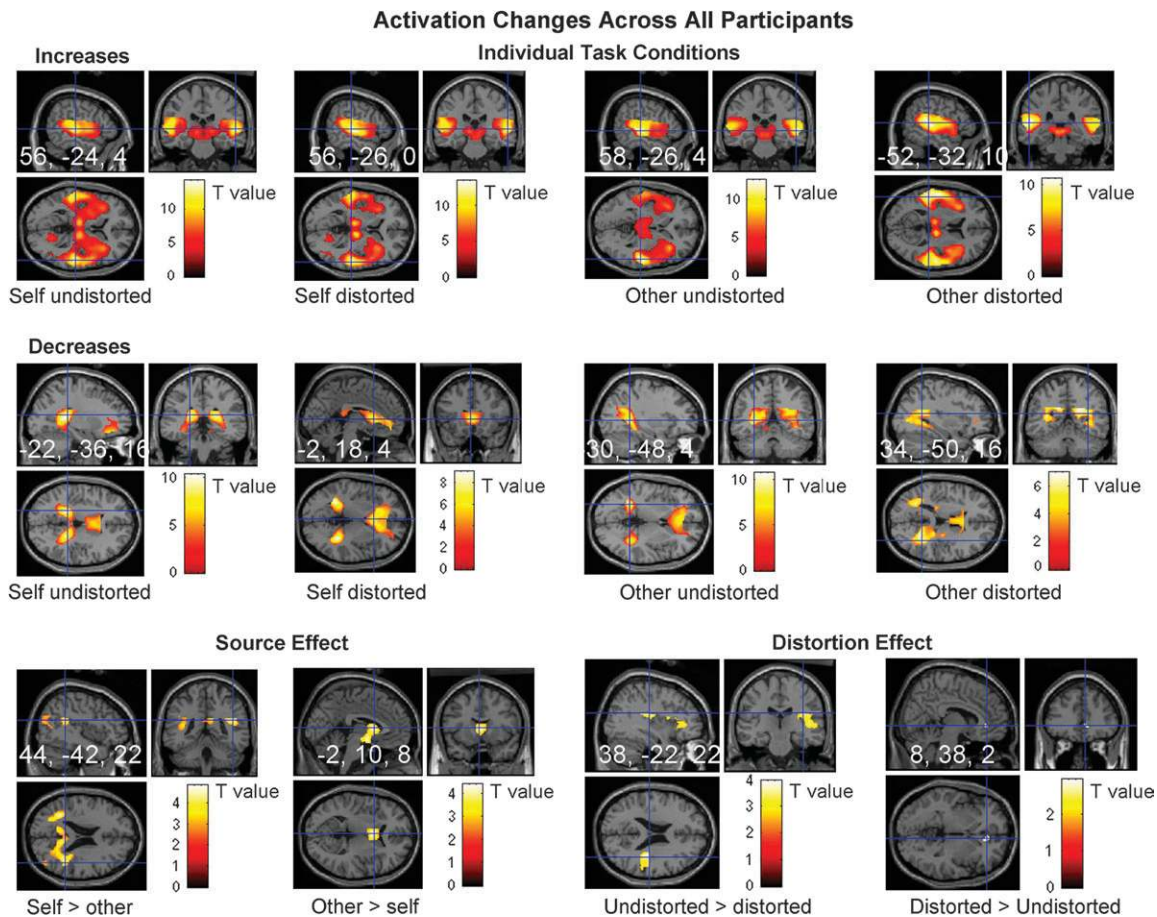


Fig. 1. Task-Related Changes in Brain Activity Across All Participants (Maps Thresholded at $P = .005$, uncorrected). The top row shows activity increases, and the middle row shows activity decreases associated with individual task conditions in sagittal, axial, and coronal views with associated Montreal Neurological Institute coordinates (x, y, z). The bottom row shows activity changes associated with source (self vs other regardless of the level of distortion) and distortion (distorted vs undistorted regardless of the source) factors. All displayed clusters, except the anterior cingulate cluster for distortion factor (distorted > undistorted), are significant ($P < .05$) after correction for multiple comparisons. Left hemisphere is shown on the left of the coronal view.

conditions involve monitoring of self-generated voice in some way. Furthermore, the performance on our task is likely to be affected not only by the ability to recognize

and discriminate between the “self” and “others”² but also to include other influences such as prior experience of having used the word stimuli facilitating recognition

Table 5. Brain Areas Showing Activation Changes for Source and Distortion Effects Across All Participants (Voxel Threshold $P = .005$)

Cluster Size (Voxels n)	Brain Region	Brodmann Area (BA)	Side	MNI Coordinates			Voxel T Value	Cluster P (Corrected for Multiple Comparisons)
				x	y	z		
2584	Self > other							
	Angular gyrus (extends to posterior cingulate)	39	R	44	-42	22	4.86	<.001
		39	L	-34	-48	20	4.75	
Precuneus	31	R	16	-52	24	4.33		
	Other > self							
956	Caudate	n/a	L	-2	10	8	4.41	.012
		n/a	n/a	0	0	-8	4.04	
1874	Undistorted > distorted							
	Transverse temporal gyrus	41	R	38	-22	22	3.97	<.001
	Inferior frontal gyurs/Insula	44	R	32	30	0	3.62	
Globus pallidus	n/a	R	20	-4	-2	3.57		
None	Distorted > undistorted							

Note: MNI = Montreal Neurological Institute; n/a = not applicable.

Table 6. Neural Activity Differentiating Groups of Good (Regardless of Diagnosis) and Poor Performers

Individual task conditions (voxel threshold $P = .005$)

Cluster Size (Voxels n)	Brain Region	Brodmann Area	Side	MNI Coordinate			Voxel T Value	Cluster P (Corrected for Multiple Comparisons)	Direction of Effects
				x	y	z			
Poor performers > good performers									
Self-un-distorted									
11038	Superior temporal gyrus, inferior frontal gyrus (extends to putamen and thalamus)	22	R	54	-24	0	7.18	<.001	Relatively stronger activity increases in good performers
		45/47	R	34	6	-2	5.78		
		22	L	-52	-36	10	5.76		
836	Middle occipital gyrus	18	L	-14	-82	14	4.89	0.013	As above
		18/19	L	-10	-96	22	4.06		
		19	L	-24	-90	28	3.62		
653	Middle occipital gyrus	18	R	16	-70	10	3.84	.032	As above
		19	R	24	-60	4	3.61		
		18	R	16	-78	14	3.44		
Self-distorted									
4523	Middle-superior temporal gyrus (extends to the thalamus and the putamen)	21	R	56	-26	2	7.25	<0.001	As above
		22	R	46	-30	12	5.32		
		6	R	56	-6	18	5.29		
3650	Superior temporal gyrus (extends to the insula and the inferior frontal gyrus)	22	L	-44	-38	14	5.06	<.001	As above
		22/42	L	-54	-26	18	4.69		
		22	L	-54	-34	16	4.62		
Other-undistorted									
1259	Superior temporal gyrus Inferior parietal cortex	22	L	-52	-40	14	6.57	.007	As above
		40	L	-52	-36	26	2.87		
1593	Middle-superior temporal gyrus	21	R	56	-28	0	6.46	.002	As above
		42	R	62	-34	6	5.27		
		22	R	52	-36	16	4.53		
Other-distorted									
5186	Precentral gyrus Insula (extends to the thalamus and the inferior frontal gyrus)	6	L	-58	-6	10	6.60	<.001	As above
		n/a	L	-38	14	-2	5.50		
		42/22	L	-58	-24	6	5.26		
6129	Superior temporal gyrus (extends to the thalamus, putamen, and the inferior frontal gyrus)	22	R	60	-26	0	6.23	<.001	As above
		22	R	62	-12	0	6.19		
		42	R	54	-22	6	5.79		
Poor performers > good performers									
Self-undistorted									
1492	Medial prefrontal/ cingulate gyrus	32	R	2	32	4	6.78	.001	Greater deactivation in good, relative to poor, performers
		11	L	-22	-28	-14	4.24		
		32	L	-14	40	6	4.08		
None									
Self-distorted									
Other-undistorted									
749	Medial prefrontal/ cingulate gyrus	32	L	-24	42	6	4.38	.045	As above
		32/24	L	-4	28	6	3.64		
831	Middle temporal gyrus (extends to PHG)	39	R	30	-52	16	4.28	.032	As above
		21	R	36	-52	8	4.02		
		23	R	28	-52	24	3.98		
Other-distorted									
1844	Posterior cingulate Inferior parietal cortex	29/30	L	-12	-52	22	5.50	<.001	As above
		40	L	-44	-66	28	4.87		

Table 6. Continued

Individual task conditions (voxel threshold $P = .005$)									
Cluster Size (Voxels n)	Brain Region	Brodmann Area	Side	MNI Coordinate		Voxel T Value	Cluster P (Corrected for Multiple Comparisons)	Direction of Effects	
Poor performers > good performers									
987	Medial prefrontal/ cingulate gyrus	24/32	R	20	32	6	3.61	.003	As above
		24	L	-6	26	6	3.49		
		24	L	-18	32	4	3.48		
Source and distortion effects (voxel threshold $P = .05$)									
Self > other									
5695	Inferior frontal gyrus	45	L	28	34	4	4.38	.015	During self compared with other—more activity in good performers. Less activity in poor performers.
	Hippocampus	N/a	R	-28	-30	-8	3.17		
	Parahippocampal gyrus	35	R	-38	-34	-8	3.10		
None	Undistorted > distorted								

Note: MNI = Montreal Neurological Institute; n/a = not applicable.

in self-generated voice, working memory (WM, remembering the feedback while making a decision), and the ability to switch between and tendency to consider various possible options while making a judgment about origin of the voices.

Neural Findings

Task-Related Activation Patterns Across All Participants. Individual Task Conditions.

Increases. We found activation of a large neural network comprised of the thalamus (MGN), superior-middle TL, and IFG with successful monitoring of own or others' voice in both distorted and undistorted conditions. There was remarkable overlap across the 4 conditions.

An important finding is the robust thalamic, especially MGN, activation. Thalamic activity has been considered necessary for conscious awareness of auditory signals.³² Specifically, the MGN is the main area of thalamic relay for ascending auditory information, receiving auditory information from the inferior colliculus via the brain stem and then relaying it to the primary auditory cortex.³³ Previous studies may have failed to observe MGN activation with this or very similar tasks, most likely because they had relatively smaller samples or did not consider relevant activation contrasts.

The activation of frontotemporal regions with successful performance is generally consistent with previous studies.^{20,27} Despite the classical view that the left TL dominates speech perception, recent studies³⁴⁻³⁷ emphasize the roles of STG and the superior temporal sulcus in both hemispheres in the auditory representation of speech.³⁸ Furthermore, areas in the right anterior superior temporal sulcus are known to show sensitivity to au-

ditory distinctiveness³⁹ required for correct attribution of auditory feedback across all conditions. The TL activations extended into the inferior parietal lobe, hypothesized to be an extension of the higher auditory association cortex.³³ The left IFG (Broca's area) activation was also expected given its role in speech and language,^{37,38} while the right IFG activation may relate to the earlier noted WM requirement of our task.⁴⁰

Decreases. The parahippocampal gyrus, PC (extending to the angular gyrus for "other" conditions), and MFG were deactivated during all conditions. These areas are involved in a "default" mode of conscious experience and often found to be deactivated during goal-specific task conditions.⁴¹

Source and Distortion. The comparison of the self with other conditions, regardless of presence or absence of distortion, revealed differential activity in the PC and angular gyrus. This effect was attributable to stronger deactivation of these areas during the other, relative to the self, conditions. The angular gyrus is involved in awareness of action authorship.⁴² The PC has been implicated in familiarity⁴³ in addition to its known involvement in a "default" mode of conscious experience.⁴¹ Such functions of the angular gyrus and PC may account for stronger deactivation of these regions during the other, relative to the self, conditions given the possible overlap between the self conditions that involved processing of own (thus familiar) voice and the default baseline state that itself may involve participants being aware of themselves in the surroundings. Judging from the performance data, the other conditions were also more difficult than the self-conditions and more difficult task conditions

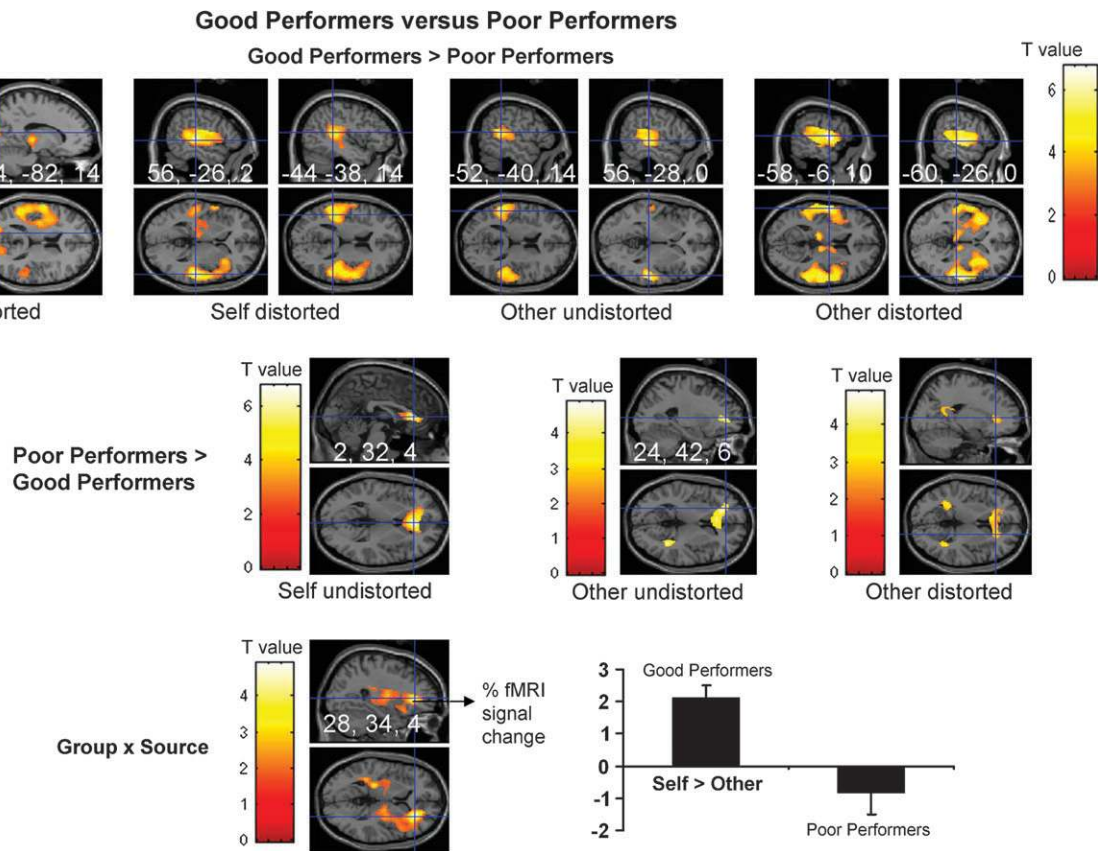


Fig. 2. Brain Activity Differentiating Good Performers (Healthy Participants and Well-Performing Patients) and Poor Performers. The top and the middle rows show group differences in activations and deactivations found in individual task condition comparisons (maps thresholded at $P = .005$ uncorrected) with associated Montreal Neurological Institute coordinates (x, y, z). The bottom row shows group \times source in sagittal and axial views effect (maps thresholded at $P = .05$, uncorrected) with associated MNI coordinates (x, y, z). All displayed clusters are significant ($P < .05$) after correction for multiple comparisons. Left hemisphere is shown on the left of the axial view.

generally produce greater deactivation. The caudate also showed differential activity between the self and other conditions; this, however, was influenced by illness and symptoms (discussed later).

A cluster located in the right transverse temporal gyrus, extending to the IFG, showed greater activity during the undistorted, compared with the distorted, conditions. Although on the surface, this effect may seem inconsistent with the finding of Fu et al.,²⁰ it was influenced by illness and symptoms. Specifically, patients and HC showed activity changes in opposite directions, and HC showed activity changes in the same direction (ie, greater activity during the distorted condition) as in the study of Fu et al.²⁰ (see further for a discussion of the effect in patients). There was some (nonsignificant) AC activity during the distorted, relative to the undistorted, feedback conditions. This is consistent with previous findings²⁰ using a longer version of this task and perhaps related to greater effort or conflict in decision making during the conditions of distorted feedback.⁴⁴

Good Performers Vs Poor Performers. As expected, poor performers showed much reduced frontotemporal

activity than good performers. Activation deficit in poor performers was most consistently localized in the superior-middle TL and appeared somewhat stronger and larger in extent on the right. This may be associated with low discrimination between self-generated vs another person's voices in poorly performing patients given the sensitivity of right TL to auditory distinctiveness.³⁹

Reduced left IFG activity in poor performers may suggest a language-related deficit.³⁸ Reduced IFG activation (in either hemisphere) could also be the cause or effect of reduced verbal WM.⁴⁰ This in our task would mean loss of information after hearing the feedback, prior to being able to make a response about its origin. Previous studies examining auditory verbal imagery have observed normal frontal but reduced TL activity in patients with schizophrenia when they were required to imagine words spoken by others.^{14,15,45,46} The auditory verbal imagery paradigms, however, may not exert the same, time-constrained, load on the verbal WM system as the current paradigm. Furthermore, the inferior frontal junction is activated in paradigms that involve task switching and set shifting,⁴⁷ and there may be a role for these functions in successful performance on our task.

Table 7. Neural Activity Differentiating Groups of Healthy Participants and Patients With Schizophrenia Regardless of Performance

Individual task conditions (voxel threshold $P = .005$)									
Cluster Size (Voxels n)	Brain Region	Brodmann Area	Side	MNI Coordinates		Voxel T Value	Cluster P (Corrected for Multiple Comparisons)	Direction of Effects	
Healthy participants > patients									
None	Self-undistorted			x	y	z	.008	Less activity in patients than healthy participants.	
942	Thalamus	n/a	R	8	-30	14	4.32		
		n/a	L	-4	-30	14	4.16		
		n/a	L	-14	-36	12	3.88		
None	Self-distorted Other-undistorted Other-distorted								
Patients > healthy participants									
Self undistorted									
997	Superior-middle temporal gyrus	22/42 21	L	-48	-36	18	4.92	.006	Relatively stronger activity in patients.
			L	-56	-28	0	3.74		
939	Superior temporal gyrus	42	R	50	-32	20	4.74	.008	As above.
		42	R	58	-28	8	3.58		
		22	R	64	-38	8	3.33		
None	Self distorted Other undistorted Other distorted								
639	Superior-middle temporal gyrus	22	L	-54	-32	10	3.95	.019	As above.
		22	L	-56	-42	16	3.86		
		21	L	-50	-40	-2	3.51		
Source and distortion effects (voxel threshold $P = .05$)									
Other > self									
5695	Hippocampus	n/a	L	-16	-38	0	3.75	.05	Deactivation during self and non-significant activation during other in patients, especially with high negative symptoms; opposite effect to some degree in healthy participants.
	Hypothalamus	n/a	R	4	-6	4	3.16		
	Ventral striatum	n/a	L	-6	10	6	3.11		
Undistorted > distorted									
6525	Superior temporal gyrus	42	R	40	-24	18	3.64	.007	More activity during undistorted relative to distorted in patients, especially with poor performance and/or positive symptoms; opposite effect to some degree in healthy participants.
	Middle temporal gyrus	21	R	36	-22	-10	3.24		
	Inferior frontal gyrus	n/a	R	42	30	12	3.15		

Note: MNI = Montreal Neurological Institute; n/a = not applicable.

Poor performers also showed thalamic (MGN, lateral GN, pulvinar) hypoactivity during 3 conditions. Although the thalamus has traditionally been seen as a relay center, recent theoretical positions⁴⁸⁻⁵⁰ and empirical data⁵¹⁻⁵³ point to the importance of these thalamic areas in stimulus-driven attention and, more generally, in cortico-cortical processing achieved by flow of information via cortico-thalamo-cortical reentry routes. Poor attention to and/or reduced cortical processing of speech stimuli may contribute to poor performance.

The finding of relatively greater activity in the medial prefrontal and posterior temporal parietal cortices in

poor performers, relative to good performers, although not specifically hypothesized, is an interesting one. As noted earlier, these areas were deactivated during active conditions and the observed difference between the poor and good performers in the medial prefrontal and the posterior temporal parietal cortices arose because of a lack of deactivation of these regions in the former group, perhaps reflecting the fact that this group activated task-relevant areas to a markedly reduced degree.⁵⁴

Finally, a significant source \times performance group interaction indicated more activity in the right lateral frontal, extending to the left hippocampal, region during the

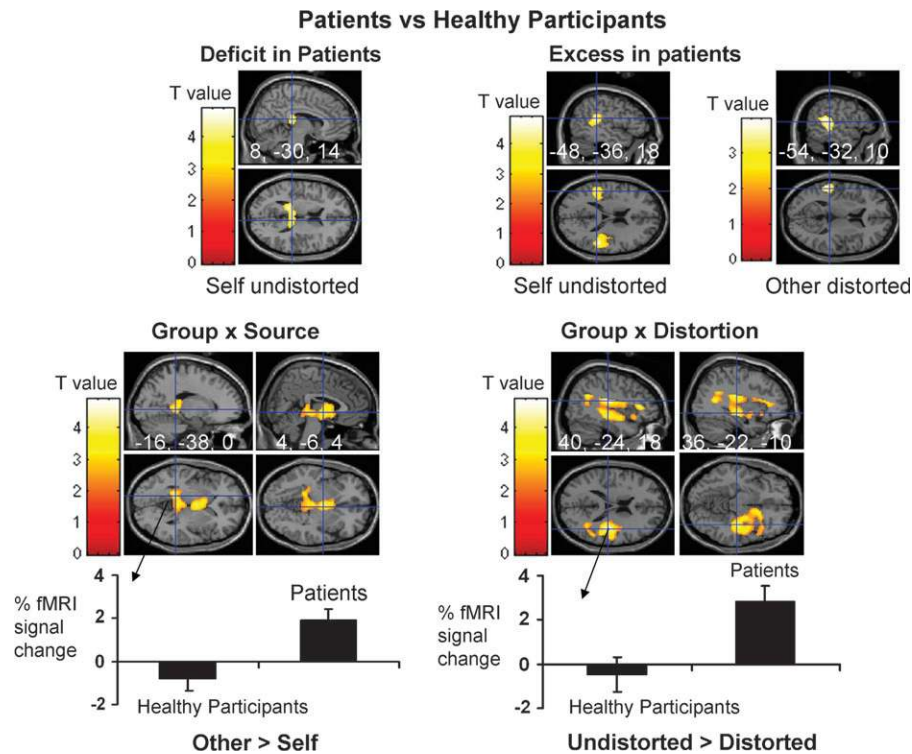


Fig. 3. Brain Activity Differentiating Patients From Healthy Participants. The top row shows group differences with individual task conditions (maps thresholded at $P = .005$ uncorrected), and the middle and bottom rows show group \times source and group \times level of distortion effects, respectively, in sagittal and axial views (maps thresholded at $P = .05$, uncorrected) with associated Montreal Neurological Institute coordinates (x, y, z). All displayed clusters are significant ($P < .05$) after correction for multiple comparisons. Left hemisphere is shown on the left of the axial view.

self, compared with other, conditions in good but not poor performers. Previous studies demonstrating coactivation of hippocampal and right inferior frontal regions during autobiographical retrieval, but not during semantic retrieval, have indicated the involvement of these areas in access of episodes from the personal past.^{55,56} Our finding thus may reflect successful recall of previous experience of having spoken and listened to (in own voice) the word stimuli in good performers.

Patients Vs Healthy Participants: Illness and Symptoms Influences. There was activation deficit in patients, unrelated to their performance or symptoms, in the thalamus (figure 3) during the self-undistorted condition. This abnormality seems located in the pulvinar region, rather than in the geniculate nucleus, suggesting perhaps that thalamic first-order relay of auditory information may not be affected by schizophrenic illness. Given the evidence for (a) strong thalamus/pulvinar involvement in attention^{57,58} and (b) impaired attention as a schizophrenia trait/risk marker,^{59,60} it may represent a trait-related effect in schizophrenia. All patients included in this study, however, were on antipsychotic drugs. Altered activation patterns found across the entire patient sample, therefore, may have also included the neurotoxic (causing, or resulting in greater, abnormality) or neuroprotective

(minimal abnormality) influences of long-term antipsychotic treatment.^{61,62} Future studies involving antipsychotic-naïve patients with schizophrenia would help to clarify this issue.

Patients, relative to HC, also showed more activity in parts of the superior-middle TL bilaterally during the self-undistorted condition and in the same area but only on the left during the other-distorted condition (figure 3). These 2 effects when combined contributed to the group \times distortion interaction showing less activity in the right temporal (extending to the IFG) region during the distorted, compared with the undistorted, conditions in patients compared with HC. The degree of negative change in the right TL activity from undistorted-to-distorted feedback associated with poor performance in patients. This may suggest that the right TL dysfunction, specific to language and voice perception network, may be particularly relevant to performance deficit in schizophrenia.⁶³ The right TL dysfunction (less activity during the distorted, compared with undistorted, conditions), supporting our hypothesis, was also associated with positive symptoms, especially hallucinations.

We also observed, for the first time to our knowledge, in patients especially those with blunted affect, emotional withdrawal, poor rapport and passive social avoidance symptoms, deactivation of the ventral striatum, midbrain

and hypothalamus during processing of own voice and (nonsignificant) activation when processing someone else's voice leading to the finding of significantly greater activity during the other, relative to self, conditions (group \times source, figure 3). The hypothalamus, thalamus, ventral striatum, and midbrain regions are activated by expectation of unpleasant stimuli in healthy people,⁶⁴ perhaps in association with autonomic arousal.⁶⁵ The hypothalamus is particularly important within the stress axis.⁶⁶ It is possible that emotionally withdrawn and socially avoidant patients perceived the whole experimental setting (including baseline conditions) and someone else's voice unpleasant (ie, stressful) and arousing unless they heard their own voice. A recent study⁶⁷ has shown greater amygdala activation to fearful faces in schizophrenia patients with (than without) flat affect and proposed limbic overstimulation with flat affect in schizophrenia. Increased limbic activity to angry and contemptuous face stimuli has been seen in generalized social phobia.⁶⁸ Dysfunctions of the mesocortical and mesolimbic pathways are proposed as being the most relevant to social anxiety.⁶⁹ Striatal dysfunction has also been noted in generalized social phobia.⁷⁰

Other Observations

Although the right TL dysfunction was associated with both poor performance and positive symptoms, we did not find significant associations between the PANSS symptom dimensions and performance. This observation deserves some discussion because self-monitoring hypothesis of schizophrenia was initially proposed to explain some of the first-rank symptoms, which presume a loss of self-agency.³ Several studies using a range of paradigms have supported the association between the symptoms of delusions of control, thought insertion, and thought blocking and poor self-monitoring^{6–8,71–75} though there are others that did not find such associations.^{21,76} Similarly, most,^{10–12,29,77} but not all,⁷⁸ studies using verbal self-monitoring paradigms observed a relationship between positive symptoms, mainly AH and delusions, and impaired self-monitoring. An association between self-monitoring deficit and positive symptoms may more often be found in acutely psychotic samples.

Conclusions

Successful monitoring of own or someone else's speech activates a large neural network comprised of the thalamic (MGN), temporal, and IFG regions that have important roles in perception and processing of auditory information and language. Reduced response, both in terms of activations in this network and deactivations in the associated "default" network involving primarily the MFG and PC, underlies impaired monitoring of self- or externally generated speech in schizophrenia. Within this population, emotionally withdrawn and so-

cially avoidant patients show greater response modulation in autonomic arousal-linked neural systems with self-vs-others distinction. Positive symptoms, especially hallucinations and persecution, and poor monitoring share a common activation abnormality in the right STG during processing of degraded speech.

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