
Cortical Responsiveness during Talking and Listening in Schizophrenia: An Event-Related Brain Potential Study

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Background: Failures to recognize inner speech as self-generated may underlie positive symptoms of schizophrenia-like auditory hallucinations. This could result from a faulty comparison in auditory cortex between speech-related corollary discharge and reafferent discharges from thinking or speaking, with misattribution of internal thoughts to external sources. Although compelling, failures to monitor covert speech (thoughts) are not as amenable to investigation as failures to monitor overt speech (talking).

Methods: Effects of talking on auditory cortex responsiveness were assessed in 10 healthy adults and 12 patients with schizophrenia (DSM-IV) using N1 event-related potentials (ERPs) to acoustic and visual probes during talking aloud, listening to one's speech played back, and silent baseline. Trials contaminated by muscle artifact while talking were excluded.

Results: Talking and listening affected N1 to acoustic but not to visual probes, reflecting modality specificity of effects. Patterns of responses to acoustic probes differed between control subjects and patients. N1 to acoustic probes was reduced during talking compared with baseline in control subjects, but not in patients. Listening reduced N1 equivalently in both groups.

Conclusions: Although the failure of N1 to be reduced during talking was not related to current hallucinations in patients, it may be related to the potential to hallucinate. *Biol Psychiatry* 2001;50:540–549 © 2001 Society of Biological Psychiatry

Key Words: Schizophrenia, self-monitoring of speech, ERPs

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Introduction

Although the symptoms of schizophrenia are diverse, attempts have been made to unify them with overarching explanatory concepts. Some have suggested that deficits at the input side, such as a “defective filter,” or gating failure, could be responsible for producing sensory overload, cognitive fragmentation, thought disorder (Braff 1993; Freedman et al 1996), and other positive symptoms of the disease. Others have suggested that deficits at the output side, such as monitoring of thoughts and action, may be responsible for symptoms such as hallucinations and delusions of alien control (Feinberg 1978; Frith 1995).

Most neurophysiologic studies of schizophrenia have focused on input deficits, observing event-related potentials (ERPs) synchronized to stimulus delivery. Although abnormalities of the early stimulus-synchronized ERP components have been related to presumed deficits in sensory gating, abnormalities of later stimulus-synchronized components have been related to attentional deficits (Ford et al 1994) and clinical symptoms (e.g., Mathalon et al 2000). One approach to assessing correlates of output is to observe ERPs synchronized to the response, allowing observation of activity preceding and following a response to a stimulus (Kopp and Rist 1999; Mathalon et al, submitted).

Output dysfunction also can be assessed by using carefully chosen sensory stimuli to probe brain function during the production and execution of responses. Our study uses the N1 (or N100) component elicited by acoustic and visual probes, presented while the subject is talking aloud, to assess auditory and visual processing differences during speech output in patients with schizophrenia. The auditory N1, and its magnetic counterpart the N1 m, is usually followed by another major response, the P2, which has not been extensively investigated. N1 is generated in auditory cortex; is evoked by transient auditory stimuli; peaks approximately 100 m/sec after stimulus onset; and has been used to study cortical processing of pure tones, noises, and speech sounds. Although generated

in the same areas of auditory cortex, the N1 sec elicited by speech and tones sometimes differ. In one study N1 was larger and later to speech sounds than to pure tones (Tiitinen et al 1999) even though it was difficult to match perfectly intensity-time envelopes for vowels and tones. N1 has a long (~10-sec) temporal recovery function, with smaller N1 sec elicited by tones with shorter interstimulus intervals (Davis and Zerlin 1966), a reduction that depends on tone onsets rather than durations (Onishi and Davis 1968). Thus, N1 to an acoustic probe will be sensitive to the presence of other competing auditory events or acoustic interference. Additionally, N1 is sensitive to attention, being smaller when attention is directed away from the eliciting stimulus (Hillyard et al 1973). Importantly, N1 to tone probes presented while the subject was instructed to listen to prerecorded speech was reduced compared with N1 sec elicited during instructions to ignore the speech (Papanicolaou et al 1988). As with the auditory N1, the visual N1 emanates from sensory cortical structures (Martinez et al 1999) and is also affected by attention, being smaller when attention is directed away from the eliciting stimulus (Han et al 2000).

Recent magnetoencephalographic (MEG) studies measuring N1 m have shown that while a subject is talking, responsiveness of the auditory cortex to 1000-Hz tone probes is dampened and delayed compared with conditions in which a subject is reading silently (Numminen et al 1999). Furthermore, responsiveness to vowel probes (Numminen and Curio 1999) and tones (Numminen et al 1999) is reduced during both talking aloud and playback of recorded speech, suggesting a role for direct acoustic interference between probes and self-generated speech. To rule out the effects of acoustic interference on responsiveness to probes presented while the subject was talking aloud, one study (Curio et al 2000) assessed responsiveness to vowel sounds as they were being spoken compared with when they were being played back. They found that responses are dampened and delayed during talking compared with during playback, and they attributed the reduction during talking to the dampening effect of the corollary discharge of the planned speech transmitted from prefrontal speech areas to temporal lobe auditory processing areas (Curio et al 2000). In addition to auditory interference and corollary discharge, attention could be affecting the N1 to probes in these experiments: played back speech may be more attention grabbing than talking, so that probes get less attention during talking than during listening. Possibly, the reduction in responsiveness to probes during both talking and listening seen earlier (Numminen and Curio 1999) resulted from a combination of two processes: responses to probes during talking might be reduced by acoustic interference and corollary discharge, and re-

sponses to probes during listening might be reduced by acoustic interference and attention to speech playback.

Corollary discharge mechanisms in sensorimotor feedback systems have been well described, whereby an initiated motor movement of limbs or eyes is associated with a corollary discharge representing the expected sensory consequences of the movement. This corollary discharge is sent to relevant sensory areas, dampening sensory response. Mechanisms could be subcortical or cortical. Subcortically, middle ear muscles contract during talking (Salamon and Starr 1963), causing a 25-dB reduction of sound transmission to the auditory nerve (Moller 1975). Perhaps through contraction of the middle ear muscles, brain-stem responses to probes are reduced during talking aloud (Papanicolaou et al 1988). Cortically, there may be an interaction between frontal and temporal lobes (Paus et al 1996; Petrides and Pandya 1988), such that a corollary discharge associated with the motor act of talking inhibits responsiveness of auditory cortex to the spoken utterance and other acoustic stimuli.

Corollary discharge may be one of the brain's most elementary mechanisms for distinguishing self-generated from externally generated sensory-perceptual events, and its dysfunction has been posited to underlie certain positive symptoms of schizophrenia, including auditory hallucinations and delusions of alien control (Feinberg 1978; Frith 1995). Current circuit-based models of brain dysfunction in schizophrenia suggesting disrupted connectivity between frontal and temporal lobes (Friston and Frith 1995) are consistent with the hypothesis of defective corollary discharge mechanisms in schizophrenia. If corollary discharge dysfunction contributes to auditory hallucinations in schizophrenia, the mechanism would involve compromise of corollary discharges associated with inner speech or internal thoughts. Although corollary discharge is typically associated with primitive sensorimotor systems, an association with thinking is plausible in that thinking in some ways is a complex motor act (Jackson 1958). It has been noted (see p. 196, Feinberg and Guazzelli 1999) that thinking "might conserve and utilize the computational and integrative mechanisms evolved for physical movement." Corollary discharge is one such mechanism.

Although theoretically compelling, the mechanisms that allow self-monitoring of covert responses such as thinking are not easily amenable to direct measurement. Our approach here was to examine the effects of producing and listening to overt speech on sensory processing of acoustic probes in schizophrenia by means of event-related brain potentials. We hypothesized that these probes would be sensitive to abnormalities in integrative feedback mechanisms in schizophrenia operating during speech production and perception, including corollary discharge deficits.

Table 1. Hallucinatory Sentences Used for Talking and Listening Conditions

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1. It makes me mad when you do that.
 2. Go for a walk to the canteen.
 3. That was really stupid.
 4. This is going to work out perfectly.
 5. Someone is listening.
 6. Tie your shoes.
 7. Get off your duff and do something.
-

Specifically, we compared responsiveness of the auditory cortex to acoustic probes while subjects spoke aloud or heard playback of statements typical of those that patients report hearing when experiencing auditory hallucinations (Nayani and David 1996; Table 1). Visual probes were used for comparison.

As with Curio and colleagues, our measure of cortical responsiveness to the acoustic probes was the N1 component of the EEG-based ERP. N1 and its MEG counterpart, N1 m, are generated in the transverse gyri of Heschl on the superior temporal gyrus of primary auditory cortex (Reite et al 1994, 1997) and the supratemporal plane of the secondary auditory cortex (Pantev et al 1995). Because of the orientation of the superior surface of the temporal lobe, the activity generated there is usually best seen at the vertex of the head in ERP studies.

To control for the effects of auditory interference during talking, we compared N1 sec elicited by probes presented while subjects were talking to N1 sec elicited by probes presented while subjects were listening to recordings of their own speech, (cf. Numminen et al 1999). Finally, to establish a baseline of cortical responsiveness, N1 sec to the probes were also elicited in the absence of speaking or listening to speech. We also recorded ERPs to visual probes containing a negative peak at the same latency as the auditory N1 to establish the specificity of the findings to the auditory modality.

Methods and Materials

Subjects

Data from 10 healthy adults (9 men and 1 woman) and 12 patients with schizophrenia (11 men and 1 woman) are presented here. All gave written informed consent after the procedures had been fully described. Normal control subjects ranged in age from 30 to 52 years (mean = 44.5, SD = 7.2), and patients ranged in age from 24 to 53 years (mean = 39.5, SD = 7.1), a nonsignificant difference ($p = .12$). Years of education were higher in control subjects (mean = 15.3, SD = 1.3) than in patients (mean = 12.7, SD = 1.0, $p < .0001$). Control subjects were recruited by newspaper advertisements and word of mouth, screened by telephone using the psychiatric screening questions from the Structured Clinical Interview for DSM-IV (SCID; First et al 1995), and were excluded for any significant history of Axis

I psychiatric illness. Patients were recruited from community mental health centers as well as from inpatient and outpatient services of the Palo Alto Veterans Affairs Health Care System. All patients met DSM-IV (American Psychiatric Association 1994) criteria for schizophrenia (six undifferentiated, four paranoid, one disorganized, and one residual) based either on the diagnosis from a SCID interview conducted by a psychiatrist or psychologist or on consensus of a SCID interview conducted by a trained research assistant and a clinical interview by a psychiatrist or psychologist. In two cases, a psychiatrist made the diagnoses by patient chart review. Nine of the patients were taking atypical and three were taking typical antipsychotic medications. Prospective patient and control participants were excluded if they met DSM-IV criteria for alcohol or drug abuse within 30 days before study; several patients had a distant history of alcohol dependence ($n = 2$), drug abuse ($n = 2$), or drug dependence ($n = 1$). In addition, patient and control participants were excluded for significant head injury (loss of consciousness greater than 30 min or resulting in neurologic sequelae) or neurologic or other medical illnesses compromising the central nervous system. All of the normal control subjects and all but two of the schizophrenic patients were right handed.

Patient symptoms were assessed by at least two trained raters (including a psychiatrist or clinical psychologist) administering the 18-item Brief Psychiatric Rating Scale (BPRS; Hedlund and Vieweg 1980; Overall et al 1967). This was done during a semistructured interview conducted on the same day ($n = 10$), within 2 days ($n = 1$), or within 1 week ($n = 1$) of ERP testing. Ratings were averaged over two raters. The mean BPRS total from the 12 patients was 38.5 (SD = 10.6; range = 21–52.5). In addition, the Schedule for Assessment of Positive Symptoms (SAPS; Andreasen 1984) was administered in the same rating session as the BPRS. To assess the relationship between ERP measures and positive symptoms of hallucinations and delusions, we used the BPRS Hallucinatory Behavior and Unusual Thought Content items as well as the SAPS global ratings of Hallucinations and Delusions.

Experimental Procedure

Before electrodes were attached, sound recordings were made of the subject saying the seven hallucinatory statements shown in Table 1 to be played back during the listening condition. While one research assistant attached the electrodes, another adjusted the intensities of each of the seven sentences by increasing or decreasing the intensity to match the loudness of a target sentence that had been recorded from another speaker until all sentences were equal in loudness. The playback intensity of the target sentence was set relative to each subject's speech perception threshold, determined by ascending and descending limits. Playback intensity of all the sentences was set at 25 dB above that threshold, a comfortable listening level of approximately 70 to 75 dB sound pressure level (C scale). During talking, participants were asked to speak at a comfortable level, which approximated the loudness of the played back sentences.

PROBE SEQUENCE. The probe sequence was presented to subjects continuously during each condition (baseline, listening

and talking) and consisted of a series of three equiprobable stimuli: speech sound (/ba/, 250-m/sec duration), noise (broad-band, 250-m/sec duration), and square checkerboard (5×5 degrees of visual angle, 250-m/sec duration), presented with three equiprobable, random stimulus onset asynchronies (0.8, 1.0, or 1.2 sec). During the baseline condition, the intensity of /ba/ and noise was set to 76 dB sound pressure level (C scale). During the talking and listening conditions, the probe loudness was adjusted upward to ensure probe discriminability and were several dB more intense than during baseline.

BASELINE CONDITION. Subjects sat upright in a comfortable chair in a sound-attenuated room, wore foam ear-cuff headphones to hear the sounds, and faced a video monitor to see the checkerboard. They were asked to keep their eyes focused on a fixation point on the screen throughout the experiment. There was no other task associated with this condition. The presentation of stimuli lasted 2 min and 42 sec.

LISTENING AND TALKING CONDITIONS. As in the baseline condition, subjects were presented with the probe sequence throughout listening and talking conditions. The first hallucinatory statement, recorded earlier, was played back repeatedly to the subjects during a 30-sec period, which allowed about seven repetitions of the statement. Next, subjects repeated the same statement aloud for another 30 sec. They were instructed to speak in their natural talking voice, neither shouting nor whispering. Performance was monitored by a research assistant who listened to the subject throughout the condition to ensure speaking was always at a normal loudness level for conversation. About one third of the subjects had to be reminded to speak louder or softer. This listen-talk sequence was repeated seven times, once for each of the seven hallucinatory statements, lasting a total of 7 min. Although there was a negative emotional valence to some of the statements, patients were told before recording that none of the statements were about them; after the session, no patients reported being troubled by the statements.

ERP Procedure

ERP RECORDING. Electroencephalogram (EEG) was recorded from 35 sites designed for a scalp topographic analysis to be presented elsewhere. Here, we report ERPs to acoustic probes collected from Fz, Cza, Cz, and ERPs to checkerboards collected from Pz. Vertical electrooculogram (VEOG) was recorded from electrodes placed above and below the right eye and horizontal (HEOG) from electrodes placed at the outer canthus of each eye. We sampled EEG and EOG every 2 m/sec. During acquisition, EEG data were band pass filtered between .05 and 40 Hz.

ERP DATA SCREENING. Data were treated as follows:

1. Trial epochs began 100 m/sec before the stimulus and ended 500 m/sec after it.
2. Each trial was subjected to linear detrending (\sim .5-Hz high pass filter).
3. Each trial was corrected for the effects of eye blinks and eye movements based on correlations of the VEOG and

HEOG with the EEG recorded at each electrode site (Gratton et al 1983).

4. The average of the 100-m/sec prestimulus baseline was subtracted from each time point in the epoch.
5. Trials with voltages exceeding $\pm 100 \mu\text{V}$ during the -100- to 300-m/sec period were excluded.

All remaining trials were subjected to visual screening by the investigators to eliminate any artifacts introduced by talking. In the data from the 10 control subjects included in this analysis, 10.1% of all trials did not pass the computer and investigator criteria, and for the 12 patients, 11.3% of the trials did not pass. (Data from eight other patients and seven other control subjects had to be excluded from these analyses because of insufficient number of trials. The included and excluded patients did not differ in clinical symptomatology; total BPRS: $t[18] = 0.996$, $p = .33$). ERP averages were filtered further before components were measured using a .5- to 15-Hz filter.

ERP COMPONENTS. N1 was identified as the most negative peak between 75 and 200 m/sec and P2 as the most positive peak between N1 and 300 m/sec. To acoustic probes, ERPs were measured at Fz, Cza, and Cz, where they were largest. To the visual probe, ERPs were measured at Pz, where they were large and less susceptible to movement artifacts than at leads O1 and O2 where visual ERPs are typically measured.

STATISTICAL ANALYSES. Repeated-measures analyses of variance (ANOVA) were performed for each component. For the acoustic probes, an initial four-way ANOVA assessed effects of Group (control subjects, patients), Condition (baseline, listening, talking), Stimulus (speech, noise), and Scalp site (Fz, Cza, and Cz). For the visual probe, an ANOVA assessed effects of Group (control subjects, patients) and Condition (baseline, listening, talking). Simple main effects of variables were reported only if they did not interact with other variables. In the case of significant interactions, the highest order interactions were parsed first, followed by lower order interactions contained within them, using subanalyses of variance. Greenhouse-Geisser (G-G) corrections were used when appropriate (see Tables 2-5).

Spearman correlations were performed to assess relationships among the N1 effects of interest with the SAPS summary scores and BPRS scales.

Results

N1 Amplitude

N1 amplitude effects can be seen in Figure 1, where grand average ERPs are plotted, and in Figure 2, where means are plotted. The results of a four-way ANOVA for Group (2) \times Condition (3) \times Acoustic Stimulus (2) \times Electrode (3) for N1 amplitude appear in Table 2. The significant effect of Stimulus was due to N1 being larger to /ba/ than to noise. The Condition \times Group interaction was parsed by testing the Condition effect in control subjects and patients separately. The Condition effect was

Table 2. Analyses of Variance of N1 Amplitude

Variable	df	F	p ^a
G	1, 20	1.44	.24
S	1, 20	9.48	.006
S × G	1, 20	1.65	.21
C	2, 40	28.67	.0001
C × G	2, 40	5.14	.01
NCS	2, 18	16.63	< .0001
B > T	1, 9	23.33	.0009
B > L	1, 9	24.46	.0008
T = L	1, 9	.07	.79
SCZ	2, 22	16.51	< .0001
B = T	1, 11	1.36	.27
B > L	1, 11	104.41	< .0001
T > L	1, 11	11.79	.006
E	2, 40	3.08	.06
E × G	2, 40	1.36	.27
S × C	2, 40	.31	.73
S × C × G	2, 40	.77	.47
S × E	2, 40	.72	.49
S × E × G	2, 40	.62	.54
C × E	4, 80	3.66	.01
Fz: B > T > L	2, 40	18.69	< .0001
Cza: B > T > L	2, 40	29.11	< .0001
Cz: B > T > L	2, 40	36.91	< .0001
C × E × G	4, 80	.40	.81
S × C × E	4, 80	.44	.78
S × E × C × G	4, 80	1.49	.21

G, group; S, stimulus; C, condition; NCS, normal control subjects; B, baseline; T, talking; L, listening; SCZ, schizophrenic patients; E, electrode; Fz, midline frontal; Cza, midline fronto-central; Cz, midline central.

^aGreenhouse-Geisser corrected as appropriate.

significant in both control subjects and patients, but the pattern of effects was different, as can be seen in Figures 1 and 2 and Table 2. N1 was larger during the talking condition than during the listening condition in patients, but not in control subjects. Furthermore, compared with baseline, N1 was not reduced during talking in patients, but was in control subjects. In both groups, N1 was reduced during listening compared with baseline. Although there was a Condition × Electrode interaction, the Condition effect was significant at each Electrode, with the effect being slightly smaller at more frontal sites.

A Group × Condition ANOVA for N1 to the checkerboard revealed no significant effects for Group [$F(1, 20) = .19, p = .67$, Condition [$F(2, 40) = 1.93, p = .17$ G-G], or the Group × Condition interaction [$F(2, 40) = .26, p = .71$ G-G].

N1 Latency

The results of a four-way ANOVA for Group (2) × Condition (3) × Acoustic Stimulus (2) × Electrode (3) for N1 latency appear in Table 3. The Stimulus × Condition interaction was parsed by assessing the Condition effect separately for both stimuli. As can be seen in Table 3,

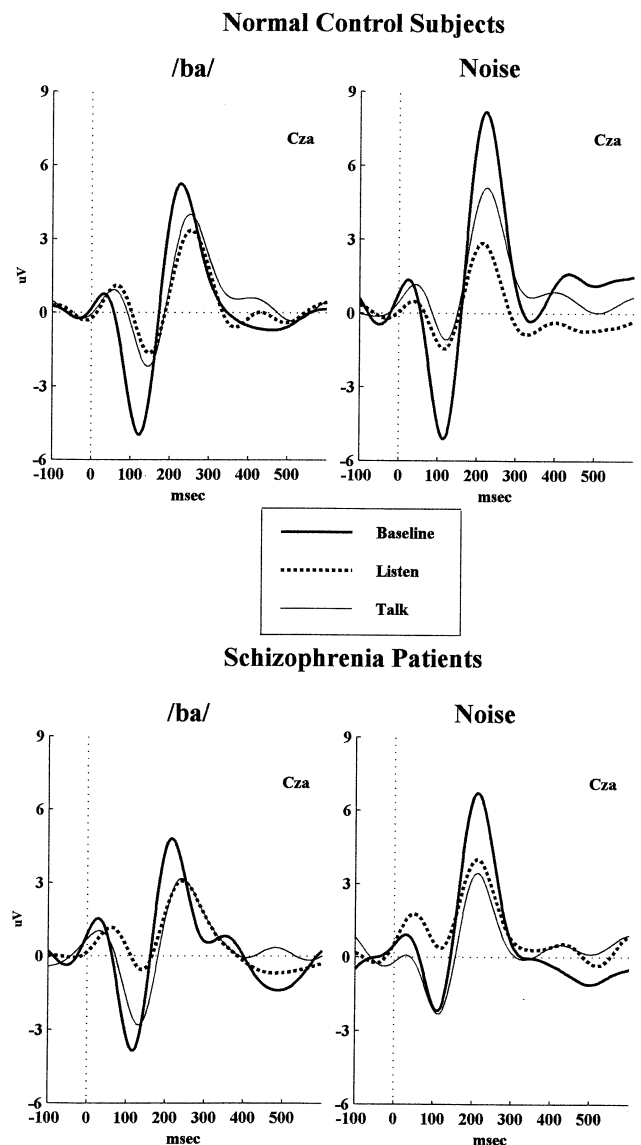


Figure 1. Event-related potentials to /ba/ and noise acoustic probes from control subjects and patients with schizophrenia during baseline, and while subjects talked aloud, or while subjects listened to played-back speech. Negativity is plotted down.

Condition significantly affected N1 to both /ba/ and noise, but the pattern of effects was different for the two stimuli (see Figure 3). Compared with baseline, talking delayed N1 to /ba/ by about 20 m/sec and to noise by about 10 m/sec; listening delayed N1 to /ba/ by about 20 m/sec also but did not delay N1 to noise. Thus, N1 to noise was only delayed during talking, whereas N1 to /ba/ was delayed during both talking and listening.

The Group × Stimulus interaction was parsed by assessing the effects of Group separately for each Stimulus. There was a significant effect of Group for N1 latency

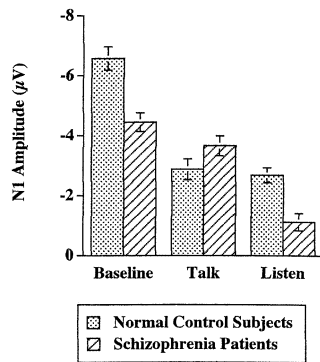


Figure 2. Means and SE of the means for N1 amplitude to acoustic probes, collapsed across type, from control subjects and patients with schizophrenia during baseline, and while subjects talked aloud, or while subjects listened to played-back speech.

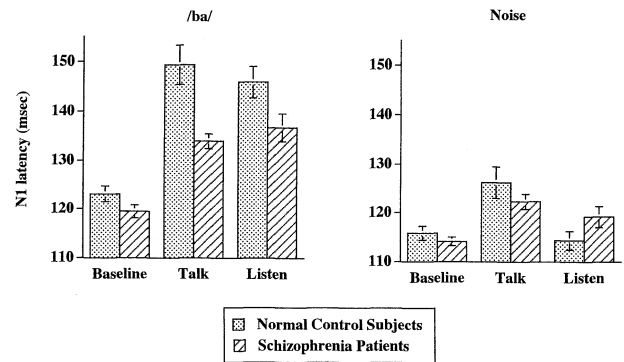


Figure 3. Means and SE of the means for N1 latency to noise and /ba/ acoustic probes from control subjects and patients with schizophrenia during baseline, and while subjects talked aloud, or while subjects listened to played-back speech.

to /ba/, with control subjects having a later N1 than patients. There was no Group effect for noise. This interaction was also parsed by assessing the effect of Stimulus for both groups separately, with N1 to /ba/ being later than to noise in control subjects ($p < .0001$) and patients ($p = .0002$).

A Group \times Condition ANOVA for N1 latency to the checkerboard revealed no significant effects: Group effect [$F(1, 20) = 1.56, p = .22$], Condition effect [$F(2, 40) = .31, p = .73G-G$], Group \times Condition interaction [$F(2, 40) = .07, p = .93G-G$].

P2 Amplitude

A Group (2) \times Condition (3) \times Acoustic Stimulus (2) \times Electrode (3) ANOVA for P2 amplitude revealed a significant main effect of Condition such that P2 to acoustic probes was largest during the baseline condition and equivalent during talking and listening (Table 4). In addition, there was a significant interaction for Condition \times Electrode; although significant at each Electrode, the Condition effect was smallest at frontal sites. Also, there was a significant main effect of Stimulus with noise eliciting a larger P2 than /ba/. Finally, there was a main effect of Electrode due to P2 being smaller at Fz than at Cz or Cza.

Unlike N1, P2 amplitude was not affected by Group or an interaction of Group with the other variables.

A Group \times Condition ANOVA for P2 amplitude to the checkerboard revealed no significant effects of Group [$F(1, 20) = .30, p = .59$] or Group \times Condition [$F(2, 40) = 1.09, p = .34G-G$]; however, Condition [$F(2, 40) = 5.60, p = .01G-G$] did affect P2, being larger during baseline than talking [$F(1, 20) = 4.00, p = .06$] and listening [$F(1, 20) = 20.69, p = .0002$] but not smaller during listening than talking [$F(1, 20) = .876, p = .36$].

P2 Latency

A Group (2) \times Condition (3) \times Acoustic Stimulus (2) \times Electrode (3) ANOVA for P2 latency revealed a significant interaction for Stimulus \times Condition and a significant main effect of Stimulus (Table 5). To understand the

Table 3. Analyses of Variance of N1 Latency

Variable	df	F	p^a
G	1, 20	2.46	.13
S	1, 20	91.50	.0001
S \times G	1, 20	7.41	.01
NCS: /ba/ > noise	2, 18	57.26	< .0001
SCZ: /ba/ > noise	2, 22	31.06	.0002
/ba/: NCS > SCZ	1, 20	5.00	.04
noise: NCS = SCZ	1, 20	.01	.92
C	2, 40	16.85	.0001
C \times G	2, 40	1.26	.29
E	2, 40	4.94	.03
E \times G	2, 40	.27	.64
S \times C	2, 40	7.98	.0035
/ba/	1, 20	19.99	< .0001
B < T	1, 20	34.10	< .0001
B < L	1, 20	33.22	< .0001
T = L	1, 20	.01	.93
noise	1, 20	4.43	.03
B < T	1, 20	6.41	.02
B < L	1, 20	.77	.39
T = L	1, 20	3.67	.07
S \times C \times G	2, 40	.97	.37
S \times E	2, 40	.75	.41
S \times E \times G	2, 40	2.26	.14
C \times E	4, 80	1.18	.31
C \times E \times G	4, 80	2.57	.10
S \times C \times E	4, 80	1.73	.19
S \times E \times C \times G	4, 80	.51	.60

G, group; S, stimulus; NCS, normal control subjects; SCZ, schizophrenic patients; /ba/, speech sound; C, condition; E, electrode; B, baseline; T, talking; L, listening.

^aGreenhouse-Geisser corrected as appropriate.

Table 4. Analyses of Variance of P2 Amplitude

Variable	df	F	p ^a
G	1, 20	.47	.50
S	1, 20	12.85	.002
S × G	1, 20	.12	.74
C	2, 40	16.90	.0001
B > T	1, 20	21.12	.0002
B > L	1, 20	37.50	< .00001
T = L	1, 20	1.08	.31
C × G	2, 40	1.72	.19
E	2, 40	8.61	.004
Fz < Cz	1, 20	4.39	.05
Fz < Cza	1, 20	50.16	< .00001
Cz = Cza	1, 20	1.99	.17
E × G	2, 40	.56	.51
S × C	2, 40	2.99	.07
S × C × G	2, 40	1.48	.24
S × E	2, 40	3.52	.07
S × E × G	2, 40	2.52	.12
C × E	4, 80	4.65	.006
Fz: B > T = L	2, 40	11.23	.0004
Cza: B > T = L	2, 40	19.14	< .0001
Cz: B > T = L	2, 40	19.45	< .0001
C × E × G	4, 80	1.02	.39
S × C × E	4, 80	2.90	.06
S × E × C × G	4, 80	1.23	.30

G, group; S, stimulus; C, condition; B, baseline; T, talking; L, listening; E, electrode; Fz, midline frontal; Cza, midline fronto-central; Cz, midline central.
^aGreenhouse-Geisser corrected as appropriate.

interaction between Stimulus and Condition, we assessed the Condition effect separately for each stimulus. Condition affected P2 latency to /ba/ but not to noise. To /ba/, P2 latency was later during listening and talking than baseline; listening and talking did not differ from each other. This is consistent with the greater delays seen for N1 to /ba/ than noise.

A Group × Condition ANOVA for P2 latency to the checkerboard revealed no significant effects for Group [$F(1, 20) = 3.14, p = .09$], Condition [$F(2, 40) = .082, p = .92$], or their interaction [$F(2, 40) = .58, p = .56$].

Clinical Correlations

Correlations of SAPS and BPRS symptom scores with N1 amplitude and latency during baseline, talking, listening, and talking minus listening were computed. None were significant.

Discussion

Talking and listening affected N1 to acoustic but not to visual probes, reflecting the modality specificity of the N1 effects. Furthermore, the pattern of responses to acoustic probes during talking and listening differed between con-

Table 5. Analyses of Variance of P2 Latency

Variable	df	F	p ^a
G	1, 20	2.33	.14
S	1, 20	21.56	.0002
S × G	1, 20	.39	.54
C	2, 40	2.47	.11
C × G	2, 40	.30	.71
E	2, 40	1.95	.17
E × G	2, 40	1.68	.21
S × C	2, 40	7.91	.005
/ba/	2, 40	6.83	.006
B < T	1, 20	10.50	.004
B < L	1, 20	14.44	.001
T = L	1, 20	.80	.38
noise	2, 40	1.03	.37
S × C × G	2, 40	.12	.80
S × E	2, 40	.08	.86
S × E × G	2, 40	.14	.80
C × E	4, 80	.38	.75
C × E × G	4, 80	.69	.55
S × C × E	4, 80	.54	.55
S × E × C × G	4, 80	.56	.54

G, group; S, stimulus; C, condition; E, electrode; /ba/, speech sound; B, baseline; T, talking; L, listening.

^aGreenhouse-Geisser corrected as appropriate.

rol subjects and patients. In control subjects, N1 to acoustic probes was reduced to an equivalent degree for both talking and listening compared with baseline. In patients, N1 to acoustic probes was smaller during listening but not during talking compared with baseline. In addition, baseline N1 amplitude was smaller in patients than in control subjects.

The fact that listening to played back speech reduced the N1 to auditory probes relative to baseline in both groups suggests that the mechanisms contributing to this N1 reduction were normal in patients with schizophrenia. Several factors could contribute to N1 reduction during listening. N1 to acoustic probes is sensitive to attentional variables, being smaller when attention is directed away from the probes (Hansen and Hillyard 1980; Näätänen 1990). Thus, the N1 amplitude to acoustic probes during the listening condition could be reduced because listening drew attention away from the probes and left fewer attentional resources available to process the probes. Quantitatively, however, this factor may be insufficient to explain the reduction of N1. In a dichotic listening experiment, direction of attention from one ear to another changed N1 by 1 μ V in normal subjects (Hillyard et al 1973), whereas for our study we need to account for a 4- μ V reduction in N1. Furthermore, the N1 reflection of attention to tones in one ear while ignoring tones in the other ear is normal in schizophrenia, only becoming abnormal when attention must be focused on a very narrow auditory channel within an ear (e.g., attending to

shorter duration, higher tones all within one ear; Michie et al 1990).

Another factor that could contribute to N1 reduction during listening compared to baseline is acoustic interference, either operating at a perceptual level as masking effects or operating at a central level as temporal recovery function effects. Acoustic interference due to perceptual masking is probably insufficient to explain our results because a recent study indicated that in the presence of a continuous masking noise, N1 amplitude to /ba/ probes is only slightly diminished (less than 1 μ V) until the intensity of the masking noise reaches the intensity of the /ba/ when it is reduced by another 2 μ V (Whiting et al 1998); however, central acoustic interference is likely to be operating during our listening condition because speech has a punctate, intermittent quality. At short (750 m/sec) but not at long (6.75 sec) interstimulus intervals, N1 amplitude reduction to discrete tones is equal in schizophrenic patients and control subjects (Roth et al 1980). Thus, given the very brief pauses characteristic of continuous speech, central temporal inhibition during played-back speech is likely to be considerable and equal in patients and control subjects.

One of the principal motivations of this study was to examine the effects of corollary discharge that according to existing theory should be activated by talking (Curio et al 2000) more in control subjects than in schizophrenic patients (Feinberg 1978; Feinberg and Guazzelli 1999; Frith and Done 1989). Evidence from this study in support of this hypothesis is mixed. The failure of N1 amplitude to be reduced during talking compared with baseline in schizophrenic patients could be taken as a sign of their lack of corollary discharge; however, if corollary discharge were operating in the control subjects, we would have expected their N1 sec to have been smaller during talking than listening, as reported by Curio et al (2000), which was not the case. The equally reduced N1 during talking and listening in control subjects might be due to separate effects: on the one hand, attention to played-back speech might act to diminish N1 to probes during listening, and on the other hand, corollary discharge might act to diminish N1 to probes during talking.

None of the explanations discussed so far have addressed the smaller N1 during baseline in the patients compared with control subjects, a 2.5- μ V effect. Anatomic, neurochemical, and functional explanations all can be posited. Anatomically, N1 could be reduced because the frontotemporal regions known to generate N1 (Näätänen and Picton 1987) are affected by schizophrenia (e.g., Sullivan et al 1998). Neurochemically, N1 could be reduced because of glutamate hypofunction associated with NMDA receptor deficits in layer V of primary

auditory cortex (Javitt et al 2000). Functionally, N1 could be reduced during baseline because of central acoustic interference associated with internal speech, the ongoing stream of consciousness, in patients with the propensity to hear voices. That is, although it is likely that both control subjects and patients engage in internal dialogue, the internal speech in patients leaks into the auditory cortex, perhaps because of the absence of a corollary discharge. In other words, the silent thoughts of schizophrenic patients may be functionally equivalent to audible voices. Thus, perhaps N1 to probes during the baseline condition is much smaller in schizophrenic patients than in control subjects because acoustic competition from ongoing thoughts in the schizophrenic patients suppresses it. It is also possible that our effects are due to an abnormality in auditory cortex itself rather than to connections between auditory cortex and other areas of the brain.

This explanation for baseline N1 reduction in patients can be elaborated to account for the N1 results during the listening and talking conditions. While listening to recorded speech, external auditory input produced equivalent suppression of N1 to auditory probes in both groups relative to their respective baselines; however, because the baseline N1 was already reduced in schizophrenia, perhaps because of “leakage” of internal thoughts into the auditory sensory input system, the addition of external auditory input further reduced the N1 in patients in an additive fashion, keeping their absolute N1 amplitude below the level of the normal control subjects in the listening condition. This additive reduction in patients may occur because what the patient hears during playback and what he is thinking are usually different and therefore not temporally coincident. In contrast, talking may effectively suppress ongoing internal thoughts in both patients and control subjects, eliminating the “noise” effect of ongoing internal thoughts in patients and creating a condition in which internal and external speech are identical and temporally coincident in both groups. Thus, talking aloud does not increase N1 suppression in patients over baseline suppression by their internal thoughts, whereas in control subjects it adds suppression not present at baseline. In effect, talking aloud temporarily equalizes responsiveness to auditory input in the two groups.

N1 and P2 were later to /ba/ than to noise, consistent with the literature (Tiitinen et al 1999) and suggesting additional processing is allocated to linguistic compared with nonlinguistic stimuli. This slowing was less pronounced in the patients, suggesting they made less distinction between speech and nonspeech sounds. N1 to both noise and /ba/ were delayed during talking and listening compared with baseline. N1 to the noise was additionally delayed by Talking compared to Listening. This is consistent with the report of Curio et al (2000), who suggested

the delay in N1 m during Talking was due to the action of the corollary discharge; however, it is unclear why we found this for the noise and not for the /ba/. Although the effect appears smaller in the patients, there was no interaction of Group and Condition.

P2, a component that is often associated with N1 but not often reported or investigated, behaved like N1 in some regards and unlike N1 in others. Unlike N1, P2 amplitude was not affected by schizophrenia or interactions with schizophrenia; however, similar to N1, P2 was affected by Condition being larger during baseline than talking and listening, suggesting the allocation of more processing resources to the probes during baseline. It is noteworthy that this P2 effect extended to the checkerboard probe; thus the condition effect on P2 to the checkerboard cannot be explained in simple terms of acoustic interference but may have an attentional component. Reduction of ERPs to visual probes during auditory attention is consistent with the literature (Hackley et al 1990). Like N1, P2 was also affected by Stimulus, being more negative to /ba/ than to noise.

Because the auditory N1 and P2 have different scalp topographies, different sources, and different latencies, it is not surprising that they might have different sensitivities to corollary discharge. If corollary discharge is dysfunctional in schizophrenia, it could be due not to a faulty structural connection between the frontal and temporal lobes but to a distortion in the timing of the communication seen best early in processing.

Both a corollary discharge theory of hallucinations and the theory that internal speech causes acoustic interference imply that ERP differences between groups are related to auditory hallucinations; however, neither N1 amplitude nor latency variables were related to the presence of auditory hallucinations or delusions during the week that ERPs were recorded. There are at least two possible explanations for this. Dysfunction may have been partially normalized by medication just to the point that hallucinations and delusions were no longer experienced. Another possibility is that these symptoms are multiply determined. For example, for a patient to report hallucinations, the internal dialogue may have to be additionally salient because of its emotional content. Furthermore, to be noted, delusions may need the addition of fear and paranoia. Medication may have ameliorated these additional factors without normalizing the mechanism responsible for the misattribution of the internal dialogue and paranoia to external sources. Thus, the N1 measures in our subjects may have been reflective of the potential to hallucinate and have delusions rather than the current state of the symptom. That is, medications may improve the symptoms but not the mechanism that makes them possible.

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References

- American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorder (DSM-IV)*. Washington, DC: American Psychiatric Association.
- Andreasen NC (1984): *Scale for the Assessment of Positive Symptoms*. Iowa City, IA: University of Iowa.
- Braff DL (1993): Information processing and attention dysfunctions in schizophrenia. *Schiz Bull* 19:233–259.
- Curio G, Neuloh G, Numminen J, Jousmaki V, Hari R (2000): Speaking modifies voice-evoked activity in the human auditory cortex. *Hum Brain Mapping* 9:183–191.
- Davis H, Zerlin S (1966): Acoustic relations of the human vertex potential. *J Acoust Soc Am* 39:109–116.
- Feinberg I (1978): Efference copy and corollary discharge: Implications for thinking and its disorders. *Schiz Bull* 4:636–640.
- Feinberg I, Guazzelli M (1999): Schizophrenia—A disorder of the corollary discharge systems that integrate the motor systems of thought with the sensory systems of consciousness [see comments]. *Br J Psychiatry* 174:196–204.
- First MB, Spitzer RL, Gibbon M, Williams JBW (1995): *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York: Biometrics Research Department.
- Ford JM, White PM, Csernansky J, Faustman WO, Roth WT, Pfefferbaum A (1994): ERPs in schizophrenia: Effects of antipsychotic medication. *Biol Psychiatry* 36:153–171.
- Freedman R, Adler LE, Myles-Worsley M, Nagamoto HT, Miller C, Kisley M, et al (1996): Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects—Human recordings, computer simulation, and an animal model. *Arch Gen Psychiatry* 53:1114–1121.
- Friston KJ, Frith CD (1995): Schizophrenia: A disconnection syndrome? *Clin Neurosci* 3:89–97.
- Frith C (1995): Functional imaging and cognitive abnormalities. *Lancet* 346:615–620.
- Frith CD, Done DJ (1989): Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. *Psychol Med* 19:359–363.
- Gratton G, Coles MGH, Donchin E (1983): A new method for off-line removal of ocular artifact. *Electroenceph Clin Neurophysiol* 55:468–484.
- Hackley SA, Woldorff M, Hillyard SA (1990): Cross-modal selective attention effects on retinal, myogenic, brainstem, and cerebral evoked potentials. *Psychophysiology* 27:195–208.
- Han S, Liu W, Yund E, Woods D (2000): Interactions between spatial attention and global/local feature selection: An ERP study. *Neuroreport* 11:2753–2758.
- Hansen JC, Hillyard SA (1980): Endogenous brain potentials associated with selective auditory attention. *Electroenceph Clin Neurophysiol* 49:277–290.
- Hedlund JL, Vieweg BW (1980): The Brief Psychiatric Rating

- Scale (BPRS): A comprehensive review. *J Operational Psychiatry* 11:48–64.
- Hillyard SA, Hink RF, Schwent VL, Picton TW (1973): Electrical signs of selective attention in the human brain. *Science* 182:177–180.
- Jackson JH (1958): *Selected Writings of John Hughlings Jackson* [edited by J Taylor]. New York: Basic Books.
- Javitt DC, Lindsley CE, Schroeder CE (2000): NMDA-mediated neurophysiologic deficits in schizophrenia (ans) *Biol Psychiatry* 47:173S.
- Kopp B, Rist F (1999): An event-related brain potential substrate of disturbed response monitoring in paranoid schizophrenic patients. *J Abnorm Psychol* 108:337–346.
- Martinez A, Anllo-Vento L, Sereno M, Frank L, Buxton R, Dubowitz D, et al (1999): Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neurosci* 2:364–369.
- Mathalon DH, Fedor M, Faustman WO, Gray M, Askari N, Menon V, Ford JM (in press): Response-monitoring dysfunction in schizophrenia: An event-related brain potential study. *J Abnorm Psychol*.
- Mathalon DH, Ford JM, Pfefferbaum A (2000): Trait and state aspects of P300 amplitude reduction in schizophrenia: A retrospective longitudinal study. *Biol Psychiatry* 47:434–449.
- Michie PT, Fox AM, Ward PB, Catts SV, McConaghy N (1990): Event-related potential indices of selective attention and cortical lateralization in schizophrenia. *Psychophysiology* 27:209–227.
- Moller AR (1975): The function of the middle ear. In: Keidel WD, Neff WD (editors). *Handbook of Sensory Physiology, Vol 1: Auditory Systems*. Berlin: Springer, 401–519.
- Näätänen R (1990): The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behav Brain Sci* 13:201–232.
- Näätänen R, Picton T (1987): The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology* 24:375–425.
- Nayani TH, David AS (1996): The auditory hallucination: A phenomenological survey. *Psychol Med* 26:177–189.
- Numminen J, Curio G (1999): Differential effects of overt, covert and replayed speech on vowel-evoked responses of the human auditory cortex. *Neurosci Lett* 272:29–32.
- Numminen J, Salmelin R, Hari R (1999): Subject's own speech reduces reactivity of the human auditory cortex. *Neurosci Lett* 265:119–122.
- Onishi S, Davis H (1968): Effects of duration and rise time of tone bursts on evoked V-potentials. *J Acoust Soc Am* 44:572–591.
- Overall JE, Hollister L, Pichot R (1967): Major psychiatric disorders. A four-dimensional model. *Arch Gen Psychiatry* 16:146–151.
- Pantev C, Bertrand O, Eulitz C, Verkindt C, Hampson S, Schuierer G, Elbert T (1995): Specific tonotopic organizations of different areas of the human auditory cortex revealed by simultaneous magnetic and electric recordings. *Electroenceph Clin Neurophysiol* 94:26–40.
- Papanicolaou A, Wilson G, Busch C, DeRego P, Orr C, Davis I, Eisenberg H (1988): Hemispheric asymmetries in phonological processing assessed with probe evoked magnetic fields. *Int J Neurosci* 39:275–281.
- Paus T, Perry DW, Zatorre RJ, Worsley KJ, Evans AC (1996): Modulation of cerebral blood flow in the human auditory cortex during speech: Role of motor-to-sensory discharges. *Eur J Neurosci* 8:2236–2246.
- Petrides M, Pandya DN (1988): Association fiber pathways to the frontal cortex from the superior temporal region of the rhesus monkey. *J Comp Neurol* 273:52–66.
- Reite M, Adams M, Simon J, Teale P, Sheeder J, Richardson D, Grabbe R (1994): Auditory M100 component 1: Relationship to Heschl's gyri. *Brain Res Cogn Brain Res* 2:13–20.
- Reite M, Sheeder J, Teale P, Adams M, Richardson D, Simon J, et al (1997): Magnetic source imaging evidence of sex differences in cerebral lateralization in schizophrenia. *Arch Gen Psychiatry* 54:433–440.
- Roth WT, Horvath TB, Pfefferbaum A, Kopell BS (1980): Event related potentials in schizophrenics. *Electroenceph Clin Neurophysiol* 48:L27–L39.
- Salamon B, Starr A (1963): Electromyography of middle ear muscles in man during motor activities. *Acta Neurol Scand* 39:161–168.
- Sullivan E, Lim K, Mathalon D, Marsh L, Beal D, Harris D, Hoff A, Faustman W, Pfefferbaum A (1998): A profile of cortical gray matter volume deficits characteristic of schizophrenia. *Cereb Cortex* 8:117–124.
- Tiitinen H, Sivonen P, Alku P, Virtanen J, Naatanen R (1999): Electromagnetic recordings reveal latency differences in speech and tone processing in humans. *Brain Res Cogn Brain Res* 8:355–363.
- Whiting KA, Martin BA, Stapells DR (1998): The effects of broadband noise masking on cortical event-related potentials to speech sounds /ba/ and /da/. *Ear Hear* 19:218–231.