



Corollary discharge dysfunction in schizophrenia: Can it explain auditory hallucinations?

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Abstract

Failure of corollary discharge, a mechanism for distinguishing self-generated from externally generated percepts, has been posited to underlie certain positive symptoms of schizophrenia, including auditory hallucinations. Although originally described in the visual system, corollary discharge may exist in the auditory system, whereby signals from motor speech commands prepare auditory cortex for self-generated speech. While associated with sensorimotor systems, it might also apply to inner speech or thought, regarded as our most complex motor act. In this paper, we describe the results of a series of studies in which we have shown that: (1) event-related brain potentials (ERPs) can be used to demonstrate the corollary discharge phenomenon during talking, (2) corollary discharge is abnormal in patients with schizophrenia, (3) EEG gamma band coherence between frontal and temporal lobes is greater during talking than listening and is disrupted by distorted feedback during talking in normals, and (4) patients with schizophrenia do not show this pattern for EEG gamma coherence. While these studies have identified ERPs and EEG gamma coherence indices of the efference copy/corollary discharge system and documented abnormalities in these systems in patients with schizophrenia, we have so far had limited success in establishing a relationship between these neurobiologic indicators of corollary discharge abnormality and reports of hallucinations in patients.

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1. Introduction

Auditory hallucinations are a cardinal symptom of schizophrenia, occurring in about 75% of schizophrenic patients (Nayani and David, 1996). They are experienced as voices even though no one is speaking. With hemodynamic and electrophysiological brain imaging, we have the opportunity to understand the neural mechanisms underlying this perplexing symptom. One approach to understanding auditory hallucinations is “symptom capture”, a naturalist approach which attempts to image the brain, using electroencephalography (EEG), functional magnetic resonance imaging (fMRI), or positron emission tomography

(PET), as patients are experiencing hallucinations. While this approach is conceptually simple, it is extremely difficult in practice because it relies not only on the timely occurrence of an illusive subjective experience but also on the ability of the patient to reliably report its initiation and completion. Symptom capture requires patience from the research team and cooperation and insight from the patient. Nevertheless, a number of investigators have used it successfully, variously reporting that auditory hallucinations are associated with activation of speech production areas (Dierks et al., 1999), primary (Dierks et al., 1999) and secondary auditory cortices, and various polymodal association cortices (Dierks et al., 1999; Shergill et al., 2000; Silbersweig and Stern, 1996).

A more mechanistic approach that does not rely on timing, patience, cooperation and endurance is the “fundamental deficit” approach (see Silbersweig and Stern, 1996). The first step in this approach is to identify a fundamental

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psychological mechanism that when disrupted could cause auditory hallucinations. The second step is to identify the neurobiological process underlying the psychological process, and the third step is to assess the integrity of this neurobiological mechanism. First, following a suggestion of Frith (1987), we identified the self-monitoring deficit as the fundamental dysfunctional psychological mechanism responsible for auditory hallucinations. The underlying assumption is that if voices that come from inside the head (i.e., thoughts) are not identified as self-generated through a failure of self-monitoring, they will be experienced as coming from an external source (i.e., hallucinations). Next, we adopted the proposal of Feinberg (1978) who suggested that self-monitoring deficits in schizophrenia reflect dysfunction of the efference copy/corollary discharge mechanism. Then we sought a neurobiological assay of this efference copy/corollary discharge mechanism. And finally, we attempted to relate abnormalities in this assay to auditory hallucinations.

2. Efference copy/corollary discharge

Von Holst and Mittelstaedt (1950) and Sperry (1950) suggested that motor actions are accompanied by an efference copy of the action which sends a “corollary discharge” signal to sensory cortex, signaling that impending sensations are self-initiated or self-generated. In the visual system, this system may serve to stabilize the visual image during eye movements, maintaining visuo-spatial constancy. In the somatosensory system, it may explain why we cannot tickle ourselves (Blakemore et al., 1998). In its simplest form, the efference copy/corollary discharge

mechanism works to suppress perception of events that result from a self-generated action. Thus, in addition to serving as a mechanism for learning and fine-tuning our actions, it may allow an automatic distinction between internally and externally generated percepts.

3. Efference copy/corollary discharge in the auditory system

A similar mechanism may exist in the auditory system: corollary discharges from motor speech producing regions in the frontal lobes prepare the auditory cortex for perceiving resulting speech as self-generated (Creutzfeldt et al., 1989). Support for this mechanism comes from a study (Creutzfeldt et al., 1989) in which recordings were made during a pre-surgical planning procedure from the exposed surface of the right and left temporal cortices while patients talked and listened to others talking. Different populations of neurons in both the superior (STG) and middle temporal gyri (MTG) responded when the patients were hearing their own speech than when hearing the speech of others. About one third of MTG neurons and some STG neurons showed reduced responsiveness to self-produced speech. Another study (Muller-Preuss and Ploog, 1981), this time with monkeys, also described differential responses of STG to self- and other-generated vocalizations. Of particular interest was the suppression of on-going cortical activity during self-vocalization. Further, more than half of the STG neurons were reduced in responsiveness during vocalization.

Although corollary discharge is typically associated with sensorimotor systems, its application to thinking,

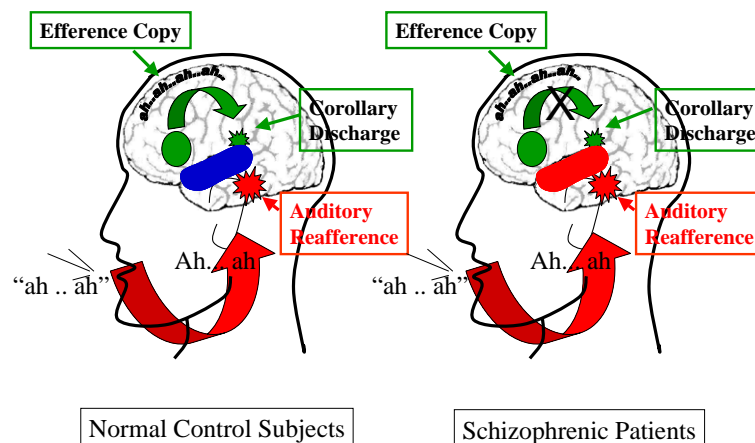


Fig. 1. Two schematics showing normal operation of the hypothesized efference copy/corollary discharge mechanism during talking (left) and its possible dysfunction in schizophrenia (right). The plan to speak originates in the frontal lobes and is shown as a green circle near Broca's area. It sends an efference copy (green ribbon) of the thought or planned sounds to the auditory cortex where it becomes a corollary discharge (green splash). At the same time, or perhaps milliseconds later, talking is initiated and the speech sounds arrive (red ribbon) at auditory cortex as the auditory reafferent (red splash). If the corollary discharge matches the auditory reafferent the sensory experience is cancelled or reduced in its impact. The auditory cortex is colored blue (left) to represent normal suppressed responsiveness to the self-produced sound when it matches the corollary discharge. In the schematic on the right, the schizophrenic patient has an X through the efference copy, and marks the auditory cortex in red to demonstrate that activity of auditory cortex is not suppressed during talking.

considered by some as “our most complex motor act” (Jackson, 1958), is plausible. Indeed, it has been postulated (see Feinberg and Guazzelli, 1999, p. 196) that thinking “might conserve and utilize the computational and integrative mechanisms evolved for physical movement”. In Fig. 1 we illustrate the concept of the efference copy/corollary discharge.

4. Efference copy/corollary discharge in schizophrenia

These early studies of cortical activation and deactivation in monkey and human, using direct recordings of neuronal activity, are consistent with more recent, non-invasive, hemodynamic brain imaging studies. Studies of healthy volunteers comparing hemodynamic activation when subjects generate words to activation when they simply repeat words have shown that word generation results in relatively more activation of frontal lobe structures and relatively less activation (relative “deactivation”) of temporal lobe structures than simple word repetition (Frith et al., 1991; Warburton et al., 1996). Importantly, temporal lobe structures are activated, not deactivated during auditory verbal hallucinations in “symptom capture” studies of patients with schizophrenia (Dierks et al., 1999; Shergill et al., 2000). Furthermore, Dierks et al. found frontal lobe (Broca’s area) activation during auditory hallucinations. This is indirect evidence that the corollary discharge from the frontal speech areas is not working to inform the temporal lobes that the input is self-generated.

It has been suggested that failures of corollary discharge may contribute to the positive symptoms of schizophrenia (Feinberg, 1978; Feinberg and Guazzelli, 1999). If an efference copy of an intended action (or thought) does not produce a corollary discharge of the expected experience, patients may fail to distinguish between their own thoughts and externally generated voices, resulting in passivity experiences or auditory verbal hallucinations (see Fig. 1).

In this report we describe the results of a series of studies using electrophysiological techniques to probe the brain during self-generated speech. These studies had the following aims: (1) to demonstrate normal operation of the corollary discharge phenomenon during talking using event-related brain potentials (ERPs), (2) to demonstrate abnormality of ERP indices of corollary discharge in patients with schizophrenia, (3) to assess EEG gamma band coherence between frontal and temporal lobes as an additional neurobiological index of corollary discharge during talking by showing that it is greater during talking than listening and is disrupted by distorted feedback during talking, (4) to demonstrate the abnormality of EEG gamma band coherence indices in patients with schizophrenia, and (5) to relate failures of these neurobiological indices of the efference copy/corollary discharge system to auditory hallucinations in schizophrenia.

5. Aims 1 and 2: use ERPs to demonstrate normal corollary discharge mechanism during speech and show that it is abnormal in schizophrenia

5.1. Introduction

To assess the corollary discharge during talking we adapted a procedure first reported by Curio et al. (2000) in which we elicited ERPs to speech sounds as they were being produced. Details of this study appear in an earlier report (Ford et al., 2001b).

5.2. Subjects

Eight medicated patients with schizophrenia (DSM-IV (SCID¹) (First et al., 1995) and 8 healthy adult comparison subjects (SCID screened for any significant history of Axis I psychiatric illness) participated in the study. All gave written informed consent after procedures had been fully explained. Prospective patient and control participants were excluded if they met DSM-IV criteria for alcohol or drug abuse within 30 days prior to study. In addition, patient and control participants were excluded for significant head injury (loss of consciousness greater than 30 min or resulting in neurological sequelae) or neurological or other medical illnesses compromising the central nervous system.

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. Controls were recruited by newspaper advertisements and word-of-mouth, and screened by telephone using the psychiatric screening questions from the Structured Clinical Interview for DSM-IV.

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), and the Schedule for Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS) (Andreasen, 1984). This was done during a semi-structured interview conducted typically on the same day or within the same week of ERP testing. Ratings were averaged over two raters.

5.3. ERP procedure

5.3.1. ERP recording

Electroencephalogram (EEG) was recorded from various scalp sites but only ERPs recorded from the subset of scalp sites where auditory ERPs are typically largest are presented here. Vertical electro-oculogram (VEOG) was recorded from electrodes placed above and below the right eye, and horizontal (HEOG) from electrodes placed at the outer

¹ In a few cases, a psychiatrist made the diagnoses by patient chart review.

canthus of each eye. EEG and EOG were sampled every 2 ms. During acquisition, EEG data were band-pass filtered between 0.05 and 40 Hz. The EEG signal elicited by the speech sound was processed using a variety of techniques to enhance signal to noise ratio and minimize noise due to artifacts associated with eye movements and speech. Technical details are available in the original reports.

5.4. Task

For the Talking condition, subjects uttered syllables [a] and [ei] for about 3 min, after they had been instructed about how loud (comfortable speaking level) and how often (syllable frequency = 1/1.5 s, probability of [a] = 0.80) to say the syllables. On average, patients uttered 121 and controls uttered 118 vowels. For the Listening condition, each subject listened to a recording of their own self-generated vowel sequence, played back to them through head phones after first adjusting the gain to equalize loudness during playback and talking. EEG epochs of 1 s were synchronized to speech onset, eye-blink corrected, and further screened to exclude speech-related artifacts during speaking. About half the trials passed these artifact rejection screens and were included in the ERP averages. ERPs were collapsed across [a] and [ei] and filtered (2–8 Hz) to reduce speech-related artifacts that might affect our measurement of N1. N1 amplitude was measured as the maximum negativity between 40 and 180 ms.

5.5. Results

Effects of talking and listening on N1 amplitude to speech sounds differed in patients and comparison subjects (Group \times Condition \times Electrode Site: $F(2,24) = 5.69$,

$p < 0.02$, two-tailed), with the Group \times Condition interaction only being significant at Cz ($F(1,12) = 4.83$, $p < 0.05$, two-tailed). This interaction was due to a smaller N1 to vowels during talking than during listening in the control subjects (paired $t(6) = -2.04$, $p = 0.04$, one-tailed), but not in the patients (paired $t(6) = 0.84$, $p = 0.22$, one-tailed). In the patients, N1 during talking was not smaller than during listening, as can be seen in Fig. 2.

5.6. Discussion

In this study, the normal subjects produced smaller N1s to vowels during talking than during listening. This is consistent with previous findings (Curio et al., 2000) and provides neurophysiological evidence in support of a speech-related corollary discharge suppressing responsiveness of auditory cortex to self-generated speech sounds. Patients did not show this reduction in N1 to their own utterances, suggesting that this mechanism of auditory cortex suppression is dysfunctional in schizophrenia.

6. Aim 3: demonstrate that gamma band coherence between frontal and temporal lobes is greater during talking than listening and is disrupted by distorted feedback

6.1. Introduction

ERP evidence from the experiment described above and others in this series (Ford et al., 2001a,b) suggests that auditory cortical responsiveness is reduced during talking and inner speech. We assume this is due to a corollary discharge from frontal speech production areas to speech

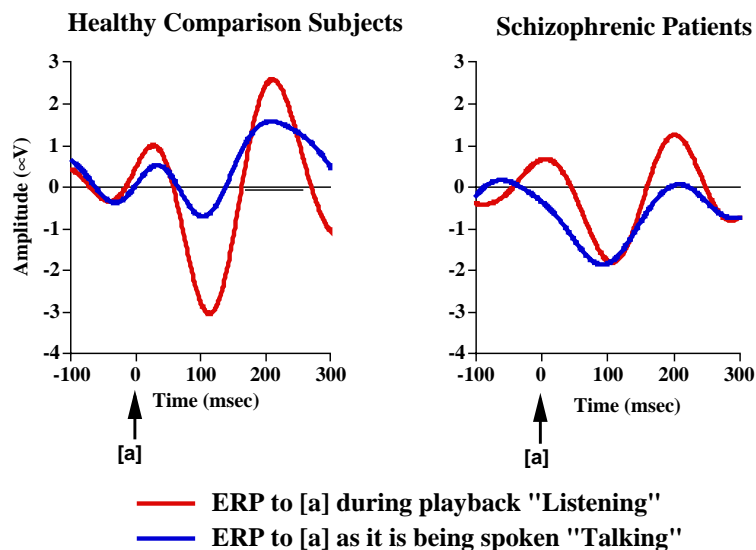


Fig. 2. ERPs recorded at Cz to the speech sounds as they are being produced (Talking, blue lines) and during playback of the same sounds (Listening, red lines). As expected, auditory cortical responsiveness is dampened during talking compared to listening in the controls, but not in the patients. ERPs were filtered with a 2–8 Hz band-pass filter.

reception areas in the temporal lobe. However, we have no direct evidence that the frontal lobe is involved. To assess the involvement of frontal speech areas, we compared the degree of inter-relatedness of the electroencephalogram (EEG) recorded over frontal and temporal lobes during talking and listening, using EEG coherence algorithms. Coherence is a frequency-dependent measure of the degree of relatedness between EEG recorded over two different brain areas. High EEG coherence between two brain areas indicates that EEG amplitudes at a given frequency and their associated phase angles are correlated across time epochs (Lachaux et al., 1999). Low EEG coherence between two brain areas indicates that EEG amplitudes at a given frequency and/or the relative phase difference between them are inconsistent across time epochs. However, the coherence measure does not specify whether the relationship between the two signals is best characterized in terms of relative phase or power (Lachaux et al., 1999). Nor does it distinguish positive from negative correlations between frequency amplitudes across time. Accordingly, it can reflect either inhibition or excitation of connected areas (Manganotti et al., 1998). Details of algorithm and method appear in an earlier report (Ford et al., 2002).

6.2. Subjects

Twenty-one healthy adults (14 men, 7 women), ranging in age from 25 to 55 years (mean=41.9, S.D.=7.2) participated in the study. All gave written informed consent after the procedures had been fully described. They were recruited by newspaper and internet advertisements as well as word-of-mouth and screened by telephone using the psychiatric screening questions from the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Subjects were excluded for any significant history of Axis I psychiatric illness, significant head injury (loss of consciousness greater than 30 min or resulting in neurological sequelae) or neurological or other medical illnesses compromising the central nervous system. All were right-handed.

6.3. Experimental procedure

6.3.1. Pre-testing and instrumentation

Before the study began, each subject was trained to say [a] with minimal movement artifact while sound equipment recording levels were adjusted to document the loudness of their average speaking level. An exemplar [a] was chosen for conversion to Neuroscan .SND format, down-sampled to 22,050 Hz and used to calibrate the sound system so that playback would be 15 dB SPL (C scale) above their average speaking level at the headphone. No output level exceeded 100 dB SPL. Subjects were also familiarized with different levels of pitch-shifted feedback used in the experiment. These included their unaltered (No Distortion) voice, their voice pitch-shifted downward by a half semi-tone (Half

Semi-Tone), and their voice pitch-shifted down by a whole semi-tone (One Semi-Tone).

The different feedback conditions were generated using an audio presentation system, linked to a personal computer equipped with sound processing software and hardware. The speech signal was picked up by microphone, sent to the computer where it was pitch-shifted, amplified, and played back to the subject via headphones, essentially in real time. Feedback was modulated to match the incoming audio signal in amplitude and duration. The average duration of the subjects' vocalizations was approximately 350 ms. The system also inserted a trigger code into the EEG data collection system.

6.3.2. Task

Two experiments, Predictable Speech Distortion and Unpredictable Speech Distortion, were conducted in a counter-balanced order. Only data from the Predictable Distortion experiment are presented here. For the *Talking condition*, subjects uttered the syllable [a] about every 1–2 s. The feedback sounds they heard over earphones were either No Distortion, Half Semi-Tone shifted, or One Semi-Tone shifted, presented in three continuous blocks of about 60 trials each. The order of blocks was randomized across subjects. For the *Listening condition*, recorded feedback sounds from the Talking condition were played back, in the same order, and subjects were instructed to simply listen. Loudness was the same in the Talking and Listening conditions.

6.3.3. EEG recording

EEG data were collected from 40 sites on the scalp, all referenced to the nose. To reduce the complexity of the data, we analyzed EEG coherence only between frontal and temporal–parietal electrodes within each hemisphere. Thus, we report data from electrodes placed over left (F7) and right (F8) inferior frontal regions in the vicinity of “Broca’s area”, and over left (CP3, CP5, P3, P5) and right (CP4, CP6, P4, P6) temporo-parietal regions in the vicinity of “Wernicke’s area”, as well as posterior auditory cortex. Vertical electro-oculogram (VEOG) was recorded from electrodes placed above and below the right eye, and horizontal EOG (HEOG) from electrodes placed at the outer canthus of each eye. EEG and EOG were sampled at 1000 Hz continuously and band-pass filtered between 0.05 and 50 Hz. EEG data were epoched from – 100 ms to 923 ms around the onset of the spoken syllable [a], for a total of 1024 ms. Individual epochs were 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). Epochs were rejected from analysis if voltages exceeded $\pm 100 \mu\text{V}$. All remaining samples were subjected to visual screening by the investigators to remove trials with incorrect/inaccurate sound triggers, and trials with gross noise contamination including excessive alpha activity, transient spikes, muscle activity or

subject movement. On average, 38 trials (60%) remained in the analysis.

6.3.3.1. Analysis of EEG coherence. To translate data from the time domain to the frequency domain, a fast Fourier transform was calculated on all 1024 data points across the 1024 ms epoch. We report coherence data for 5 sub-bands of gamma frequencies between 21 and 48 Hz, calculated in 1 Hz bins: Gamma25 (20.51–28.31 Hz), Gamma30 (28.32–33.19 Hz), Gamma35 (33.2–38.08 Hz), Gamma40 (38.09–42.96 Hz), and Gamma 45 (42.97–47.84 Hz). Coherence was calculated as the spectral cross-correlation between two electrodes normalized by their power spectra (NeuroscanLabs, 1999) for four left-hemisphere pairs (F7–CP5, F7–CP3, F7–P5, F7–P3) and four right-hemisphere pairs (F8–CP6, F8–CP4, F8–P6, F8–P4). The coherence values for each electrode pair following each stimulus were averaged to produce 8 average event-related coherence values. These were the dependent variables in the five separate analyses of variance (ANOVAs), one for each of the gamma frequency sub-bands.

6.3.4. Statistical analyses

Four-way repeated measures ANOVAs were performed on the average event-related coherence values for the 8 frontal–temporal electrode pairs listed above, for each of the 5 sub-bands. There were 4 factors: Condition (Talk/Listen), Distortion (No Distortion, Half Semi-Tone, One Semi-Tone), Hemisphere (Left, Right), and Temporal Site (CP3/4, CP5/6, P3/4, P5/6). Follow-up tests between means were conducted using planned contrast tests using the pooled error term. Huyn–Feldt epsilon corrections for non-sphericity were used to evaluate all F ratios for effects involving two or more degrees of freedom. In addition, we compared gamma coherence during the Talking and Listen

conditions for each level of distortion and each electrode pair using paired t -tests.

6.4. Results

As can be seen in Fig. 3, gamma band coherence for the sub-bands, Gamma30, Gamma35, Gamma40, and Gamma45 was greater during Talking than during Listening, and this effect was reduced when the sound produced during Talking (auditory refference) was distorted. This impression was confirmed by significant interactions between Talk/Listen and Distortion obtained from the four-way ANOVA for Gamma30, Gamma35, Gamma40, and Gamma45 (Table 1).

There was also a significant main effect of Talk/Listen for each sub-band, with coherence being greater during Talking than Listening. This effect was especially strong for the F7–CP3 pair (Talk/Listen \times Temporal Site interactions). A main effect of Temporal Site revealed that coherence was greatest for the F7–CP3 electrode pair, perhaps because of the small inter-electrode distance. It is important to note that this inter-electrode distance effect on coherence did not affect our primary finding of greater distortion effects during Talking than Listening, as the Talk/Listen \times Distortion \times Site interaction was not significant for any of the sub-bands. There was no main effect of Distortion for any sub-band.

Planned comparisons between the different levels of distortion during the Talking condition revealed that frontal–temporal gamma coherence was reduced for One Semi-Tone Distorted speech feedback compared to No Distortion feedback for Gamma40 and Gamma35, and by a Half Semi-Tone Distortion compared to No Distortion feedback for Gamma35. Of note, the mastoid bone imposes a natural low-pass filter making sounds more “self-like” or veridical when pitch is slightly shifted down, as with the half semi-tone pitch shift (Shuster and Durrant, 2003).

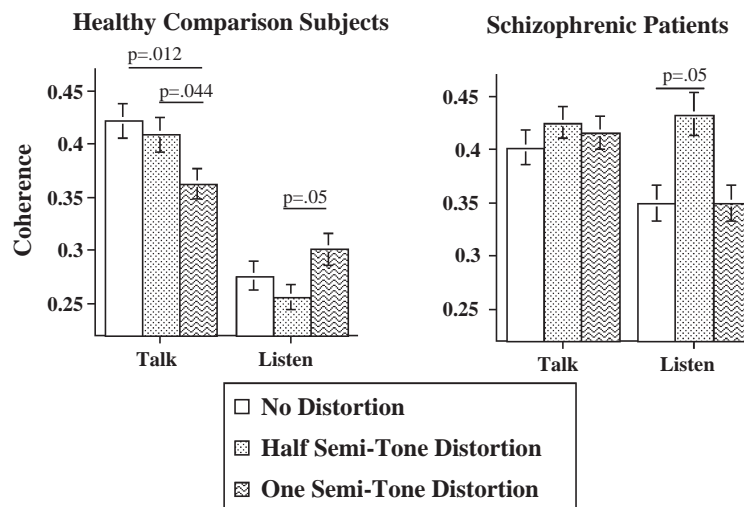


Fig. 3. Coherence values for Gamma35 during Talking and Listening when self-produced sounds were heard as spoken (no distortion), distorted a half semi-tone, and distorted one semi-tone. Values for control subjects appear on left and those for patients on the right.

Table 1
Four-way analysis of variance for gamma coherence between frontal (F7, F8) and temporal sites

Source	Gamma25			Gamma30		Gamma35		Gamma 40		Gamma 45	
	df	F-value	H–F	F-value	H–F	F-value	H–F	F-value	H–F	F-value	H–F
<i>Healthy control subjects</i>											
Distortion (Veridical, Half Semi-Tone, One Semi-Tone)	2,40	0.67	0.52	1.01	0.37	0.64	0.54	0.82	0.45	0.53	0.57
Hemisphere (Left, Right)	1,20	0.04	0.84	0.11	0.75	0.31	0.58	0.44	0.52	0.22	0.64
Temporal Site (CP3/4, CP5/6, P3/4, P5/6)	3,60	51.36	0.00	28.00	0.0001	23.03	0.0001	25.34	0.0001	26.64	0.0001
Condition (Talk/Listen)	1,20	12.59	0.00	7.36	0.01	8.48	0.01	9.33	0.01	13.51	0.0015
Distortion * Hemisphere	2,30	0.54	0.59	0.24	0.76	0.32	0.73	1.40	0.26	0.06	0.91
Distortion * Temporal Site	6,120	0.41	0.80	0.96	0.44	1.56	0.19	0.66	0.64	0.51	0.77
Hemisphere * Temporal Site	3,60	0.12	0.91	0.37	0.70	0.28	0.77	0.17	0.88	0.19	0.83
Distortion * Condition	2,40	1.30	0.28	3.55	0.04	5.20	0.01	3.68	0.03	3.96	0.03
Hemisphere * Condition	1,20	0.22	0.65	0.28	0.60	0.00	0.98	0.07	0.80	0.10	0.75
Temporal Site * Condition	3,60	7.14	0.00	4.94	0.01	9.06	0.0006	9.41	0.0002	8.37	0.0004
Distortion * Hemisphere * Temporal Site	6,120	1.17	0.33	0.53	0.62	1.56	0.20	1.25	0.30	0.78	0.54
Distortion * Hemisphere * Condition	2,40	0.59	0.56	0.45	0.64	0.06	0.94	0.13	0.85	0.49	0.59
Distortion * Temporal Site * Condition	6,120	0.46	0.77	0.88	0.47	0.70	0.58	0.32	0.85	0.28	0.89
Hemisphere * Temporal Site * Condition	3,60	0.26	0.79	0.54	0.58	0.38	0.64	1.56	0.21	1.07	0.36
Distortion * Hemisphere * Temporal Site * Condition	6,120	0.19	0.91	0.08	0.97	0.03	1.00	0.45	0.75	1.15	0.34
<i>Schizophrenic patients</i>											
Distortion (Veridical, Half Semi-Tone, One Semi-Tone)	2,38	1.102	0.34	1.49	0.24	1.48	0.24	3.43	0.04	2.13	0.13
Hemisphere (Left, Right)	1,19	2.341	0.14	1.68	0.21	1.21	0.29	0.91	0.35	0.82	0.38
Temporal Site (CP3/4, CP5/6, P3/4, P5/6)	3,57	50.651	0.0001	23.35	0.0001	21.70	0.0001	22.84	0.0001	21.27	0.0001
Condition (Talk/Listen)	1,19	0.565	0.46	0.41	0.53	0.40	0.54	1.10	0.31	1.52	0.23
Distortion * Hemisphere	2,38	1.762	0.20	1.13	0.31	0.34	0.62	0.69	0.46	1.09	0.32
Distortion * Temporal Site	6, 114	1.008	0.41	2.33	0.08	0.37	0.86	0.59	0.67	0.44	0.74
Hemisphere * Temporal Site	3,57	0.464	0.67	0.21	0.85	0.38	0.73	1.51	0.23	1.51	0.23
Distortion * Condition	2,38	0.409	0.64	1.26	0.29	0.45	0.64	1.27	0.29	0.56	0.57
Hemisphere * Condition	1,19	4.833	0.04	2.99	0.10	3.83	0.07	2.73	0.11	2.34	0.14
Temporal Site * Condition	3,57	6.132	0.01	5.52	0.01	5.48	0.01	4.44	0.01	4.33	0.01
Distortion * Hemisphere * Temporal Site	6,114	1.257	0.29	0.55	0.68	0.44	0.79	0.57	0.71	0.20	0.92
Distortion * Hemisphere * Condition	2,38	0.561	0.52	0.46	0.56	0.67	0.46	1.35	0.27	0.51	0.52
Distortion * Temporal Site * Condition	6,114	1.151	0.34	0.52	0.71	1.07	0.37	0.55	0.69	0.31	0.79
Hemisphere * Temporal Site * Condition	3,57	0.609	0.56	0.89	0.43	3.34	0.05	2.47	0.10	3.66	0.03
Distortion * Hemisphere * Temporal Site * Condition	6,114	1.1	0.36	0.23	0.94	0.31	0.88	0.11	0.98	1.30	0.28

Nevertheless, there were linear trends in the means across the different levels of Distortion during Talking for Gamma35 ($p < 0.02$), Gamma40 ($p = 0.04$), and a trend for Gamma45 ($p < 0.10$). None of the pair-wise comparisons between level of distortion were significant for Gamma30, or Gamma45 during Talking.

Planned comparisons between different levels of distortion during Listening revealed that coherence was somewhat greater to the sounds that were distorted by a whole semi-tone than those distorted by a half semi-tone or that were veridical, as can be seen in Fig. 3.

We compared gamma coherence during Talking to coherence during Listening for each electrode pair at each level of distortion. The resulting t -values and probability levels are portrayed graphically in Fig. 4, for Gamma35. Coherence during Talking was greater than during Listening when the sounds were not distorted or only distorted by half a semi-tone in 15 of the 16 electrode pairs tested.

6.5. Discussion

These data will be discussed together with those obtained from the patients described below.

7. Aim 4: demonstrate gamma band coherence during talking is not disrupted by distorted feedback in patients

7.1. Introduction

Schizophrenia is associated with self-monitoring failures, perhaps due to failures of efference copy/corollary discharge mechanism (Feinberg, 1978; Feinberg and Guazzelli, 1999; Frith, 1987). Accordingly, in the current study, we predicted that coherence in the gamma band would be less sensitive to mismatches between the expected and actual sounds during talking in patients with schizophrenia.

7.2. Subjects

Data from 20 patients with schizophrenia (20 men, 1 woman) are added to the analysis described above. All gave written informed consent after the procedures had been fully described. Patients ranged in age from 21 to 67 years (mean = 40.6, S.D. = 10.0), a non-significant difference from the controls ($p = 0.66$). Years of education were higher in controls (mean = 15.4, S.D. = 1.43) than in patients (mean = 13.7, S.D. = 1.95), a significant difference

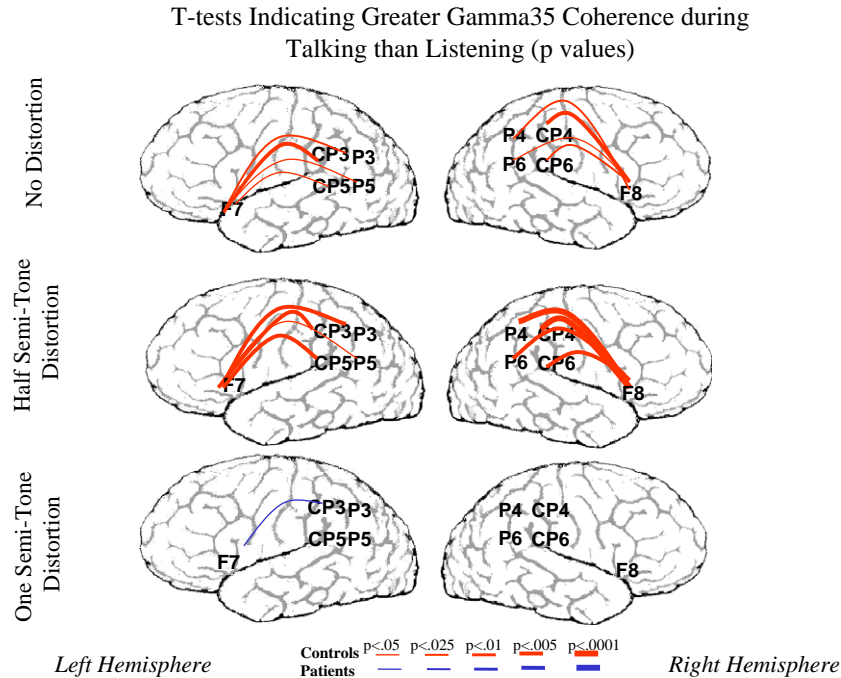


Fig. 4. Lateral cartoons of left and right hemispheres on which are drawn lines linking frontal (F7) to various temporal recording sites for the three conditions (No Distortion, top; Half Semi-Tone, middle; and One Semi-Tone, bottom). Red lines represent controls, blue lines represent schizophrenic patients. The thickness of the line represents the probability levels for *t*-tests showing greater Gamma35 coherence during talking than during listening. Thicker lines indicate greater coherence during talking than listening. In controls, coherence during talking was greater than during listening when speech was not distorted and when it was only distorted a half semi-tone.

($p < 0.001$). Patients were recruited from community mental health centers, as well as from inpatient and outpatient services of the Veterans Affairs Palo Alto Health Care System. All patients met DSM-IV criteria for schizophrenia based on the diagnosis from a SCID interview conducted either by a psychiatrist or psychologist. Patient and control participants were excluded for significant head injury (loss of consciousness greater than 30 min or resulting in neurological sequelae) or neurological or other medical illnesses compromising the central nervous system. All normal controls and schizophrenic patients were right-handed.

7.3. Results

There was a significant Talk/Listen \times Distortion \times Group interaction ($p = 0.05$), but only for Gamma35. The means for this interaction are plotted in Fig. 3. This interaction was parsed by performing four-way ANOVAs for the two groups separately. Within the patients, the Talk/Listen \times Distortion interaction was not significant, nor was there a main effect of Talk/Listen as can be seen in Table 1. Planned comparisons between the different levels of distortion revealed that frontal–temporal coherence was not affected by Distortion during Talking, but it was during Listening, with greatest coherence to the sound distorted by half a semi-tone compared to no distortion. As with the controls, there was a Talk/Listen \times Temporal Site interaction ($p = 0.009$), with the strongest Talk/Listen effect occurring

for the F7–CP3 pair, where coherence tends to be greatest, as revealed in a main effect of temporal site.

As predicted, coherence was less sensitive to mismatches during Taking than during Listening in the patients, except when the sound was distorted one semi-tone, for one electrode pair, as can be seen in Fig. 4.

7.4. Discussion of Aims 3 and 4

The capacity for the brain to reorganize itself to deal with long-term sensory distortion has been well demonstrated for the visual system by studies in which subjects wearing prism goggles learn eventually to adjust to a visually distorted world (Welch, 1978). With auditory distortion there are also short-term and longer-term adaptations. In the short term, subjects tend to make noticeable, but unconscious, adjustments to their speech in order to better match the sound they are producing with the sound they are experiencing (Houde and Jordan, 1998). In the long run, repeated exposures to distorted auditory feedback may lead to a revision of the anticipated auditory consequences of vocalization, in effect updating the “corollary discharge” signal that prepares the auditory cortex for the impending auditory reafference associated with speaking. Such neuroplastic accommodations to long-term speech alteration may be a natural occurrence during adolescence when vocal cord maturation leads to voice changes. In our study, subjects were precluded even from short-term adaptation because the distortion blocks only lasted about 2 min.

Because our sensory world is far richer and more complex than our nervous system can process and appreciate, we need a top-down mechanism to simplify bottom-up sensory processing. This mechanism may incorporate efference copies of the motor commands that predict the sensory consequences (corollary discharge) of the action (Sperry, 1950) (Von Holst and Mittelstaedt, 1950). Frontal–temporal gamma synchrony during speech may reflect the successful operation of this system. Gamma band synchrony may indeed reflect a “binding of expectation with experience” (Singer, 1999). Disruption in this synchrony may signal the frontal lobe regions that subserve speech vocalization to implement sensorimotor adaptation routines (Houde and Jordan, 1998) and may facilitate revision of the anticipated auditory consequences of vocalization.

The difference in event-related gamma-band coherence between talking and listening seen in controls was not seen in the patients, corroborating other functional brain imaging reports of a disconnection between frontal and temporal lobes in schizophrenia (e.g., Fletcher et al., 1999; Friston and Frith, 1995; Friston et al., 1995; Norman et al., 1997). These coherence data are consistent with our ERP reports (Ford et al., 2001a,b,c) and augment them by suggesting that there is an interdependence between these areas during talking, which is somewhat disrupted in patients. This finding, however, differs somewhat from our earlier report (Ford et al., 2002) where we reported an interaction between Group and Talk/Listen for the theta band, but not the gamma band. Several differences between the current study and our earlier one could possibly explain this discrepancy: (1) In the earlier study, we did not synchronize EEG to the onset of sounds as they were being produced, but to the onset of external auditory probes. By synchronizing to self-produced speech in the current study, estimations of talking-related coherence may have been optimized. (2) We used a mastoid reference in the earlier study and a nose reference in the current study, although it is not clear how and why this would make a difference. (3) The larger sample size in the current study ($n=21$) than in the earlier one ($n=12$) may have given us greater power to see the effects of talking and listening.

While others have reported that patients with schizophrenia have impaired ability to recognize their own voices when distorted (Johns et al., 2001), we believe this is the first report of gamma-band insensitivity in patients to distorted speech while talking. It may reflect a deficit in the efference copy/corollary discharge mechanism that helps us to (1) anticipate the sensory consequences of our own actions, (2) efficiently process what we experience, (3) rapidly detect discrepancies between our experience and our expectations, and (4) implement instantaneous sensorimotor adaptations to bring our experience and expectations into alignment. Thus, a failure in this mechanism could have far-reaching effects including

difficulties in language learning and motor awkwardness, and may contribute to symptoms in schizophrenia including auditory hallucinations, delusions, and formal thought disorder.

8. Aim 5: relate efference copy/corollary discharge abnormalities in patients to auditory hallucinations

In the ERP experiment described above, for which we had only 8 subjects, we attempted to relate the severity of auditory hallucinations to the amplitude of N1 during talking and to the difference in N1 during talking and listening. We also classified patients as those with almost no experience of hallucinations and those who had moderately severe hallucinatory experiences. Neither approach produced relationships between hallucinations and our N1 measures of corollary discharge dysfunction.

In the EEG coherence experiment described above, we had a larger sample (21 patients) and sought once more to relate symptoms (7 measures) to Gamma35 coherence (16 measures). To capture the effect of talking vs. listening on gamma coherence, we subtracted coherence during listening from that during talking for each of the 4 electrode pairings for both hemispheres, resulting in 8 coherence difference scores. To capture the effect of distortion on gamma coherence, we subtracted coherence during distorted feedback from coherence during no distortion (no distortion–half semi-tone; no distortion–one semi-tone), again for the 4 electrode pairings for both hemispheres, to produce another 8 coherence difference scores for each of the two difference scores (16 measures). We used the following symptom measures from the BPRS: Hallucinatory Behavior, Unusual Thought Content, Conceptual Disorganization, and Symptom Total and from the SAPS: Voices Commenting, Voices Conversing, and Hallucinations Summary. None of the correlations was significant.

To achieve a more stable estimate of symptoms, we averaged the scores from BPRS and from SAPS. To achieve a more stable estimate of coherence effects, we averaged the 4 coherence scores within each hemisphere. Again, no correlations were significant. As with the first experiment, we also broke our group into hallucinators and non-hallucinators, and again, found no relationships.

8.1. Conclusions

Dysfunction of the efference copy/corollary discharge mechanism may be a fundamental deficit in schizophrenia, and it may underlie a failure to monitor reality. It could even compromise the ability to make sensorimotor adaptations in schizophrenia and thus contribute to motor awkwardness and various other positive and negative symptoms of schizophrenia. To date, however, we have not been able to demonstrate a clear relationship between

neurobiological indicators of dysfunctional corollary discharge and the extent to which a patient currently reports experiencing auditory hallucinations.

One reason for the lack of association could be the normalizing effects of medication on the symptom but not the mechanism that makes them possible. Thus our EEG and ERP measures may reflect the potential for hallucinations rather than their current manifestation. Another reason may be an unknown contribution of hallucinations experienced during the experiment to our measures. If a patient were hallucinating during the experiment this may activate frontal and temporal lobe structures (Dierks et al., 1999) in a way that would affect the N1 response to external sounds (see Strik et al., 2004, IOP abstracts). This might only affect responses during listening, as patients report not hearing voices when they themselves are talking. In any case, it is difficult to know how concurrent hallucinations would affect our ERP and EEG data and our ability to see relationships with symptom severity during the time surrounding the study.

Alternatively, auditory hallucinations may not be the result of aberrant perceptions of inner speech from frontal speech areas, but arise from aberrant perceptions of thoughts, memories, or even “internal noises” arising from multiple distributed sources that may produce inappropriate discharges in auditory cortex or are ineffectively inhibited in auditory cortex. To the extent that these “non-speech” internal signals are themselves associated with efference copies that normally inhibit their perception through corollary discharge in auditory cortex, the breakdown in the efference copy/corollary discharge mechanism that we have described may still contribute to hallucinations in schizophrenia. However, talking may be a poor proxy for thoughts and voices. Perhaps, more studies are needed in which inner speech or thoughts are manipulated and their effects quantified using various brain imaging methods.

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References

- Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms. University of Iowa, Iowa City, IA.
- Blakemore, S., Rees, G., Frith, C., 1998. How do we predict the consequences of our actions? A functional imaging study. *Neuropsychologia* 36 (6), 521–529.
- Creutzfeldt, O., Ojeman, G., Lettich, E., 1989. Neuronal activity in the human lateral temporal lobe: II. Responses to the subject's own voice. *Experimental Brain Research* 77, 476–489.
- Curio, G., Neuloh, G., Numminen, J., Jousmaki, V., Hari, R., 2000. Speaking modifies voice-evoked activity in the human auditory cortex. *Human Brain Mapping* 9 (4), 183–191.
- Dierks, T., Linden, D., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., et al., 1999. Activation of Heschl's Gyrus during auditory hallucinations. *Neuron* 22 (3), 615–621.
- Feinberg, I., 1978. Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophrenia Bulletin* 4 (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. *British Journal of Psychiatry* 174, 196–204.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders. Biometrics Research Department, New York State Psychiatric Institute, New York, NY.
- Fletcher, P., McKenna, P.J., Friston, K.J., Frith, C.D., Dolan, R.J., 1999. Abnormal cingulate modulation of fronto-temporal connectivity in schizophrenia. *NeuroImage* 9 (3), 337–342.
- Ford, J.M., Mathalon, D.H., Kalba, S., Whitfield, S., Faustman, W.O., Roth, W.T., 2001a. Cortical responsiveness during inner speech in schizophrenia: an event-related brain potential study. *American Journal of Psychiatry* 158, 1914–1916.
- Ford, J.M., Mathalon, D.H., Kalba, S., Whitfield, S., Faustman, W.O., Roth, W.T., 2001b. Cortical responsiveness during talking and listening in schizophrenia: an event-related brain potential study. *Biological Psychiatry* 50, 540–549.
- Ford, J.M., Mathalon, D.H., Heinks, T., Kalba, S., Roth, W.T., 2001c. Neurophysiological evidence of corollary discharge dysfunction in schizophrenia. *American Journal of Psychiatry* 158, 2069–2071.
- Ford, J.M., Mathalon, D.H., Whitfield, S., Faustman, W.O., Roth, W.T., 2002. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biological Psychiatry* 21, 485–492.
- Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? *Clinical Neuroscience* 3 (2), 89–97.
- Friston, K.J., Holmes, A., Poline, J.B., Price, C.J., Frith, C.D., 1995. Detecting activations in PET and fMRI: levels of inference and power. *NeuroImage* 4, 223–236.
- Frith, C.D., 1987. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. *Psychological Medicine* 17, 631–648.
- Frith, C.D., Friston, K., Liddle, P.F., Frackowiak, R.S.J., 1991. Willed action and the prefrontal cortex in man—a study with PET. *Proceedings of the Royal Society of London. Series B, Biological Sciences* 244 (1311), 241–246.
- Gratton, G., Coles, M.G.H., Donchin, E., 1983. A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology* 55, 468–484.
- Hedlund, J.L., Vieweg, B.W., 1980. The Brief Psychiatric Rating Scale (BPRS): a comprehensive review. *Journal of Operational Psychiatry* 11 (1), 48–64.
- Houde, J.F., Jordan, M.I., 1998. Sensorimotor adaptation in speech production. *Science* 279, 1213–1216.
- Jackson, J.H., 1958. *Selected Writings of John Hughlings Jackson*. Basic Books, New York.
- Johns, L., Rossell, S., Frith, C., Ahmad, F., Hemsley, D., Kuipers, E., et al., 2001. Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. *Psychological Medicine* 31 (4), 705–715.

- Lachaux, J., Rodriguez, E., Martinerie, J., Varela, F., 1999. Measuring phase synchrony in brain signals. *Human Brain Mapping* 8, 194–208.
- Manganotti, P., Gerloff, C., Toro, C., Katsuta, H., Sadato, N., Zhuang, P., et al., 1998. Task-related coherence and task-related spectral power changes during sequential finger movements. *Electroencephalography and Clinical Neurophysiology* 109, 50–62.
- Muller-Preuss, P., Ploog, D., 1981. Inhibition of auditory cortical neurons during phonation. *Brain Research* 215, 61–76.
- Nayani, T.H., David, A.S., 1996. The auditory hallucination: a phenomenological survey. *Psychological Medicine* 26 (1), 177–189.
- NeuroscanLabs, 1999. Edit 4.1 Offline Analysis of Acquired Data: Coherence. In *SCAN™ User Guide Volume II* (pp. 128–129). Sterling, VA: Neurosoft, Inc.
- Norman, R.M.G., Malla, A.K., Williamson, P.C., Morrison-Stewart, S.L., Helmes, E., Cortese, L., 1997. EEG coherence and syndromes in schizophrenia. *British Journal of Psychiatry* 170, 411–415.
- Overall, J.E., Hollister, L., Pichot, R., 1967. Major psychiatric disorders. A four-dimensional model. *Archives of General Psychiatry* 16, 146–151.
- Shergill, S., Brammer, M., Williams, S., Murray, R., McGuire, P., 2000. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of General Psychiatry* 57 (11), 1033–1038.
- Shuster, L., Durrant, J., 2003. Toward a better understanding of the perception of self-produced speech. *Journal of Communication Disorders* 36, 1–11.
- Silbersweig, D., Stern, E., 1996. Functional neuroimaging of hallucinations in schizophrenia: toward an integration of bottom-up and top-down approaches. *Molecular Psychiatry* 1 (5), 367–375.
- Singer, W., 1999. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 24, 49–65.
- Sperry, R.W., 1950. Neural basis of the spontaneous optokinetic response produced by visual inversion. *Journal of Comparative and Physiological Psychology* 43, 482–489.
- Strik, W.K., Hubl, D., Dierks, T., 2004. Structural and functional substrates of hallucinations in schizophrenia. *International Journal of Psychophysiology* 54 (1–2), 47.
- Von Holst, E., Mittelstaedt, H., 1950. Das reafferenzprinzip. *Naturwissenschaften* 37, 464–476.
- Warburton, E., Wise, R.J.S., Price, C.J., Weiller, C., Hadar, U., Ramsay, S., et al., 1996. Noun and verb retrieval by normal subjects. studies with PET. *Brain* 119, 159–179 (Part 1).
- Welch, R.B., 1978. *Perceptual Modification: Adapting to Altered Sensory Environments*. Academic Press, New York.