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Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking

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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. We had four aims in the studies summarized in this paper: (1) to demonstrate the corollary discharge phenomenon during talking and inner speech in human volunteers using event-related brain potentials (ERPs), (2) to demonstrate that the corollary discharge is abnormal in patients with schizophrenia, (3) to demonstrate the role of frontal speech areas in the corollary discharge during talking, and (4) to relate the dysfunction of the corollary discharge in schizophrenia to auditory hallucinations. Using EEG and ERP measures, we addressed each aim in patients with schizophrenia (DSM IV) and healthy control subjects. The N1 component of the ERP reflected dampening of auditory cortex responsivity during talking and inner speech in control subjects but not in patients. EEG measures of coherence indicated inter-dependence of activity in the frontal speech production and temporal speech reception areas during talking in control subjects, but not in patients, especially those who hallucinated. These data suggest that a corollary discharge from frontal areas where thoughts are generated fails to alert auditory cortex that they are self-generated, leading to the misattribution of inner speech to external sources and producing the experience of auditory hallucinations.

Keywords: Schizophrenia; Corollary discharge; N1; EEG coherence

1. Introduction

Self-monitoring is a fundamental element of normal cognitive and motor functioning. It allows us to do on-line modifications and corrections of actions. Von Holst and Mittelstadt (1950) and Sperry (1950) suggested that motor actions are accompanied by a "corollary discharge" to sensory cortex, signaling that impending sensations are self-initiated or self-generated. In the visual system, a corollary discharge 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). It has been suggested that the corollary discharge is an efference copy of a planned action sent through a "feed forward" mechanism to the appropriate sensory cortex, preparing it for the arrival of the sensation. In its simplest form, the efference copy works to suppress perception when it results from a self-generated action. Thus, in addition to serving as a mechanism for learning and fine-tuning our actions, the efference copy may allow an automatic distinction between internally- and externally-generated percepts.

A similar mechanism may exist in the auditory system: corollary discharges from motor speech commands prepare auditory cortex for self-generated speech, linking regions of the frontal lobes where speech is generated to regions of the temporal lobes where it is heard (Creutzfeldt et al.,

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1989b; Paus et al., 1996). Creutzfeldt et al. (1989b) had patients talk and listen to others talking during a presurgical planning procedure while recording from the exposed surface of the right and left temporal cortices. Different populations of neurons in both the superior (STG) and middle temporal gyri (MTG) responded to speech when it was generated by the subject than when it was spoken by others. Muller-Preuss and Ploog (1981) recorded from monkeys and also described differential responses of STG to self- and other-generated vocalizations. Of particular interest was the suppression of ongoing cortical activity during self vocalization. About one third of MTG neurons and some STG neurons showed reduced responsiveness to self-produced speech in the Creutzfeldt et al study. In the Muller-Preuss and Ploog study, more than half of the STG neurons were reduced in responsiveness during vocalization. Although corollary discharge is typically associated with sensorimotor systems, an association with thinking is plausible, to the extent that thinking can be regarded as "our most complex motor act" (Jackson, 1958). Indeed, it has been postulated (see page 196, Feinberg & Guazzelli, 1999) that thinking "might conserve and utilize the computational and integrative mechanisms evolved for physical movement." In Fig. 1 we illustrate the concept of the corollary discharge.

These direct studies of cortical activation and deactivation in monkey and human are consistent with more recent hemodynamic brain imaging studies of word generation. In the word generation condition, subjects are presented with initial letters of words and must generate an exemplar. Compared to simple repetition of a word, generating a word results in relatively more activation of frontal lobe structures and relatively less activation (relative "deactivation") of temporal lobe structures (Frith et al., 1991, Warburton et al., 1996). However, during the experience of hearing voices when none are spoken (auditory verbal hallucinations), temporal lobe structures are *activated*, not deactivated in schizophrenics (Dierks et al., 1999, Shergill et al., 2000). 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 this mechanism may contribute to the positive symptoms of schizophrenia (Feinberg, 1978, Feinberg & Guazzelli, 1999). Specifically, if an efference copy of an intended action (or thought) is not sent to the appropriate sensory cortex, patients may fail to distinguish between their own and externally generated actions or thoughts, resulting in passivity experiences or auditory verbal hallucinations.

In this report we summarize the results of a series of studies using electrophysiological techniques to probe the brain during self-generated and inner-speech. Three of the studies used the auditory N1 to assess auditory cortical responsiveness. The auditory N1, and its magnetic counterpart the N1m, is usually followed by another major response, the P2, which has not been extensively investigated, and will not be discussed here. N1 is generated in auditory cortex by transient auditory stimuli and it reaches its peak approximately 100 ms after stimulus onset. N1 has a long (~10 s) temporal recovery function, with smaller N1s associated with shorter inter-stimulus intervals (ISI) (Davis & Zerlin, 1966). Thus, N1 to an acoustic probe will be sensitive to the presence of other competing auditory events, or acoustic interference. Addition-

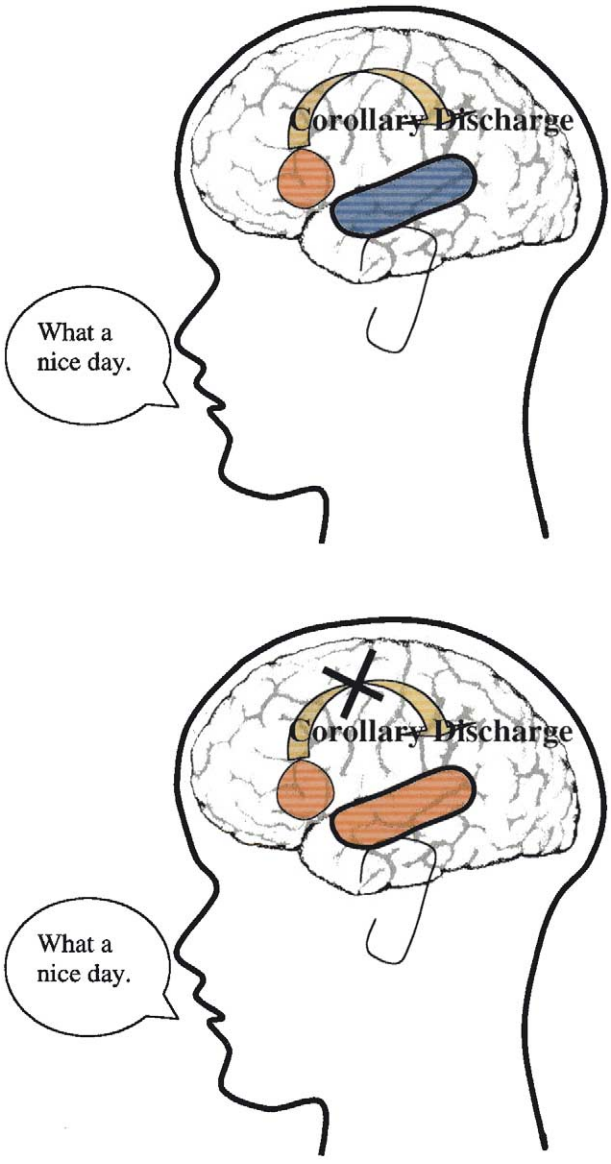

Fig. 1. Schematic showing the hypothesized corollary discharge mechanism operating during talking. It is shown going from frontal lobes, where speech is generated, to auditory cortex in the temporal lobe, where speech is perceived. On the top, the corollary discharge is shown functioning normally in a control subject; the frontal lobe is shown in red to indicate activity during talking and auditory cortex is shown in blue to indicate suppression of activity during talking. On the bottom, it is shown as functioning abnormally in a patient with schizophrenia, where activity of auditory cortex is not suppressed during talking.

ally, 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 pre-recorded speech was reduced compared to N1s elicited during instructions to ignore the speech (Papanicolaou et al., 1988). Like 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 N1m have shown that while a subject is talking, responsiveness of the auditory cortex to 1000 Hz tone probes is dampened and delayed compared to while a subject is reading silently (Numminen et al. 1999). 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 are being spoken compared to when they were being played back, a technique used by us in Experiment 2. Curio et al. found that responses are dampened and delayed during talking compared to during playback, and they attributed the reduction during talking to the dampening effect of the corollary discharge of the planned speech transmitted from pre-frontal speech areas to temporal lobe auditory processing areas.

We had four aims in these studies: (1) to demonstrate the corollary discharge phenomenon during talking and inner speech in human volunteers using event-related brain potentials (ERPs), (2) to demonstrate that the corollary discharge is abnormal in patients with schizophrenia, (3) to demonstrate the role of frontal speech areas in the corollary discharge during talking, and (4) to relate the dysfunction of the corollary discharge in schizophrenia to auditory hallucinations.

2. General methods

2.1. Subjects

Table 1 describes the patients and controls participating in each study. Medicated patients with schizophrenia (DSM-IV (SCID[1]) (First et al., 1995) and healthy adult comparison subjects (SCID screened for any significant history of Axis I psychiatric illness) participated. 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 & Vieweg, 1980, Overall et al., 1967). 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. In addition, the Schedule for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) was administered in the same rating session as the BPRS.

2.2. ERP procedure

2.2.1. 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 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 probe stimulus 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.

3. Experiment 1: responses to probes during talking

3.1. Introduction

The purpose of this study was to compare auditory cortical responsiveness to probes presented while subjects sat silently (Baseline), spoke out loud (Talking), and while they heard their speech played back to them (Listening). We predicted that responses to acoustic probes would be dampened during talking in control subjects, but not in patients. The details of this study appear in our earlier report (Ford et al., 2001c).

3.2. Procedure

Subjects participating in this experiment are described in Table 1.

[1] In a few cases, a psychiatrist made the diagnosis by patient chart review.

Table 1
Subject characteristics

	Control subjects			Schizophrenic patients		
	Studies 1 & 4 ($n=10$)	Study 2 ($n=7$)	Study 3 ($n=15$)	Studies 1 & 4 ($n=12$)	Study 2 ($n=7$)	Study 3 ($n=15$)
	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)
Gender (M/F)	9/1	7/0	13/2	11/1	7/0	13/2
Age (years)	44.5 (30–52)	35.9 (26–56)	44.7 (20–58)	39.5 (24–53)	34.1 (23–52)	40.1 (26–56)
BPRS Total	–	–	–	38.5 (21–52.5)	42.6 (19–61)	39.5 (21–52.5)
Medication (Conventional/Novel)				4/8	0/7	4/11

Three equiprobable probes, each 250 m in duration, were presented at random ISIs (0.8, 1.0 or 1.2 s): speech syllable [ba], broadband noise, and square checkerboard. During the Baseline Condition, the intensity of [ba] and noise was set to 76 dB SPL (C scale). During Talking and Listening, the probe loudness was adjusted upwards to ensure probe discriminability.

3.2.1. During the baseline condition

Subjects sat upright in 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 sequence of sounds and checkerboards. The presentation of stimuli lasted 2 min and 42 s.

3.2.2. During listening and talking conditions

The same sequence of probe stimuli was presented while subjects alternated between listening to their own prerecorded voice repeating a hallucinatory statement (e.g., "Get off your duff and do something") for 30 s followed by repeating that same statement for another 30 s. This alternation between listening and talking was repeated for seven different hallucinatory statements. Care was taken to ensure comparable intensity of recorded and spoken sentences, and subjects were trained to match their speech intensity to that of their recorded voice. This Listen/Talk sequence lasted a total of seven min. Although there was a negative emotional valence to some of the statements, patients were told before recording that none of the statements was about them, and after the session, no patients reported being troubled by the statements.

3.3. Results

The results most relevant to this review report are the differences between Talking and Baseline. Other results are reported in more detail elsewhere (Ford et al., 2001c).

Compared to Baseline, N1 was not reduced during Talking in patients, but was in controls [Group×Condition: $F(1,20)=8.21$, $P<0.01$]. This can be seen in Fig. 2. We parsed this interaction and found that N1 was smaller during Talking than during Baseline in the controls [$F(1,9)=23.33$, $P<0.001$], but not in the patients [$F(1,11)=1.36$, $P<0.27$]. A Group×Condition ANOVA for N1 to the checkerboard revealed no significant effects for Group [$F(1,20)=0.44$, $P=0.52$], Condition [$F(1,20)=1.63$, $P=0.22$] or the Group×Condition interaction [$F(1,20)=0.14$, $P=0.72$].

Correlations of SAPS and BPRS symptom scores with N1 amplitude during Baseline, Talking, and Talking minus Baseline were computed. None was significant.

3.4. Discussion

Talking 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 Baseline differed between controls and patients. In controls, N1 to acoustic probes was reduced during Talking compared to Baseline. In patients, N1 to acoustic probes was not smaller during Talking compared to Baseline. In addition, Baseline N1 amplitude was smaller in patients than in controls.

One of the principal motivations of this study was to examine the effects of corollary discharge which according to existing theory should be activated by talking (Curio et al., 2000) more in controls than in schizophrenic patients (Feinberg, 1978; Feinberg & Guazzelli, 1999; Frith & Done, 1989). By its nature, the corollary discharge happens automatically, without motivation or effort. However, our measure of cortical responsiveness, the N1 component, is minimally affected by attention, and these attention effects on N1 could possibly obscure our ability to detect the action of the corollary discharge. That is, N1 to the probe could have been reduced during talking in the controls because they found their own voices more interesting than the probe, while the opposite could have occurred in the patients.

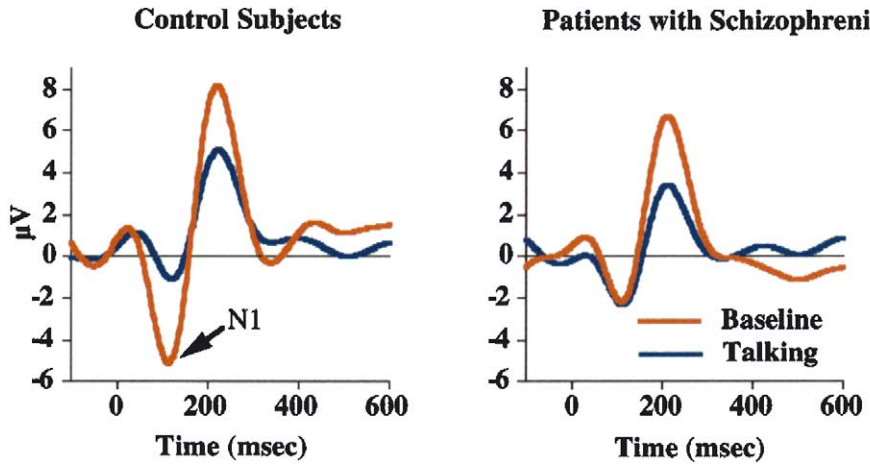

Fig. 2. Experiment 1. ERPs to an acoustic probe stimulus (noise) recorded at Cza (mid-way between Fz and Cz) are shown for controls and patients hearing the probes during a baseline condition of silence and while talking aloud. N1, generated in auditory cortical areas of the temporal lobe, is denoted with an arrow. The red lines depict auditory cortical activity to the probes during the silent baseline, and the blue lines depict auditory cortical activity to the probes during talking. In the controls, auditory cortical activity is relatively suppressed (blue) during talking compared to the silent baseline (red); this is not true in the patients. ERPs were filtered with a 0.5–15 Hz band-pass filter.

4. Experiment 2: responses to talking

4.1. Introduction

Although the effects of attention are minimal on N1, it was important to rule out the possibility of differential attention effects to probes and talking. To allow a more direct assessment of the corollary discharge during talking, we conducted the next experiment in which talking *is* the probe. That is, we assessed brain responses to talking directly, by eliciting ERPs to the speech sound as it was being produced, a procedure used by Curio and colleagues (2000). This procedure can be seen in Fig. 3. Details of this study appear in an earlier report (Ford et al., 2001a).

4.2. Procedure

See Table 1 for description of subjects included in this study.

Subjects uttered syllables [*a*] and [ei] for about 3 min, after they were 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. Each subject's self-generated vowel sequence was recorded and played back to them through head phones, after first adjusting the gain to equalize loudnesses during playback and talking. On average, patients uttered 121, and comparison subjects, 118 vowels. EEG epochs of 1 s were synchronized to speech onset, eye-blink corrected, and further screened to exclude speech-related artifacts during speaking. After artifact rejection, about half the remaining trials 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

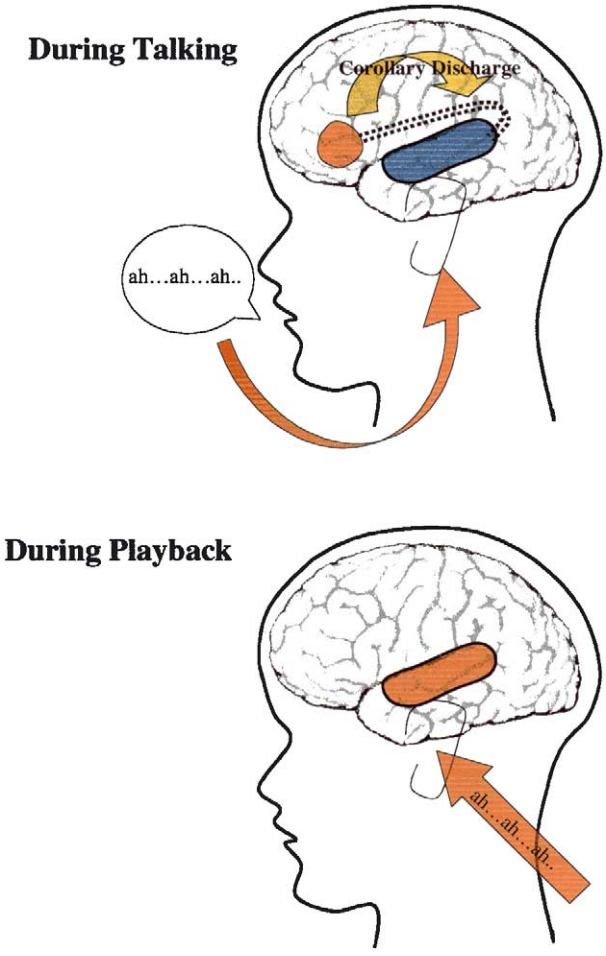

Fig. 3. Schematic illustrating the paradigm in which we compare auditory cortical responses to speech sounds as they are being produced, during talking and during playback of the same sounds.

N1. N1 amplitude was measured as the maximum negativity between 40 and 180 ms.

4.3. Results

Effects of speaking and listening on N1 amplitude to speech sounds differed in patients and comparison subjects [Group×Condition×Electrode Site: $F(2,24)=5.69$, $P<0.02$, two-tailed], with the Group×Condition interaction only being significant at Cz [$F(1,12)=4.83$, $P<0.05$, two-tailed]. This interaction was due to N1 to the vowels being smaller as they are being spoken than when they were played back 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 playback, as can be seen in Fig. 4.

4.4. Discussion

In this study, the normal subjects produced smaller N1s to uttered than played back vowels. This is consistent with previous MEG 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.

5. Experiment 3: responses to probes during inner speech

5.1. Introduction

While experiments on talking have the distinct advantage of being verifiable, our interest in the dysfunctional corollary discharge in schizophrenia is related to the experience of auditory verbal hallucinations, which is more similar to inner speech than to talking. We next asked whether inner speech might have the same effects as talking. Using the same methods we used in Experiment 1, we substituted the Talking (aloud) condition with an Inner Speech condition. Details of this experiment appear in an earlier report (Ford et al., 2001b).

5.2. Procedure

Subjects included in this experiment are described in Table 1.

Following the presentation of probes during the silent baseline condition, self-recorded hallucinatory statements, repeated for the 30 s recording were alternated with the subjects repeating that same statement silently to themselves for 30 s. This listen/inner speech sequence was repeated seven times, once for each of seven different statements and lasted seven minutes. The same random mix of vowel, noise, and checkerboard probes continued while subjects spoke aloud or silently.

5.3. Results

N1 amplitude effects are illustrated in the Fig. 5. In control subjects, N1 during baseline was larger than during inner speech [$F(1,14)=9.64$, $P=0.008$]. In patients, N1 during baseline was not significantly larger than inner speech, [$F(1,14)=2.51$, $P=0.14$]. An ANOVA for N1 to the checkerboard did not approach significance for group, condition, or group×condition.

None of the Spearman correlations between the N1 effect (i.e., baseline minus inner speech) and SAPS summary scores for hallucinations and delusions and BPRS scores for hallucinatory behavior and unusual thought content was significant.

5.4. Discussion

Using neurophysiological methods, we demonstrated that inner speech reduces responsiveness of auditory cortex in control subjects. Compared to baseline, N1 to

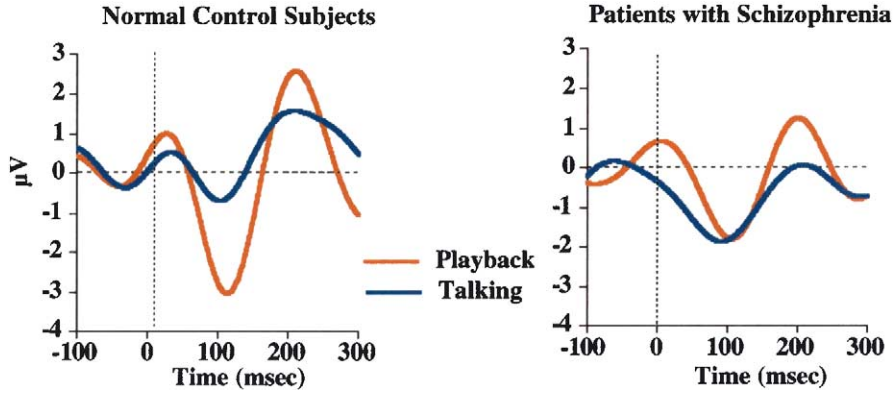

Fig. 4. Experiemtn 2. ERPs recorded at Cz to the speech sounds as they are being produced (talking, blue lines) and during playback of the same sounds (red lines). As expected, auditory cortical responsiveness is dampened during talking compared to playback in the controls, but not in the patients. ERPs were filtered with a 2–8 Hz band-pass filter.

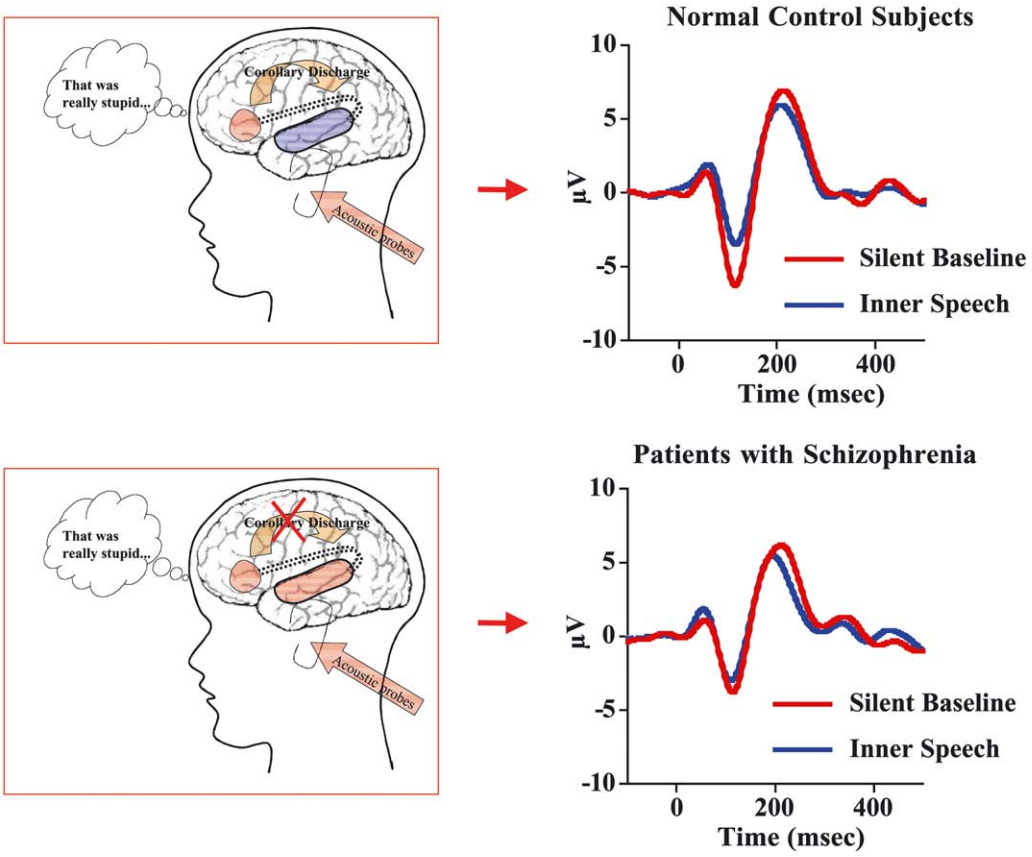

Fig. 5. Experiment 3. On the left is a schematic of our hypothesis of a dysfunctional corollary discharge mechanism in schizophrenia, and its extension to inner speech. The sentence in this figure was used in the experiment. On the right are the ERPs recorded from Cz to an acoustic probe stimulus (noise) for controls and patients hearing the probes during a baseline condition of silence (baseline) and while repeating sentences silently to themselves (inner speech). The red lines depict auditory cortical activity to the probes during the silent baseline, and the blue lines depict auditory cortical activity to the probes during inner speech. In the controls, auditory cortical activity is relatively suppressed (blue) during inner speech compared to the silent baseline (red); this is not true in the patients.

acoustic probes was reduced when control subjects were repeating sentences silently to themselves. This was not true in patients, for whom silent speech did not reduce auditory cortical responsiveness perhaps through poorly functioning corollary discharge (Feinberg, 1978). Corollary discharge may signal speech reception areas that speech-related activations are self-generated, avoiding misperceptions that these thoughts have an external source.

6. Experiment 4: EEG coherence during talking and listening

6.1. Introduction

ERP evidence from the first three experiments suggests that auditory cortical responsiveness is reduced during talking which we assume is due to a corollary discharge from frontal speech producing areas to the speech reception areas in the temporal lobe. However, we have no direct evidence that the frontal lobe is involved. To assess the role of frontal speech area involvement, we calculated the degree of inter-relatedness between frontal and temporal lobes during talking compared to 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 coherence between two brain areas indicates that their amplitudes at a given frequency *and* their associated phase angles are correlated across time epochs (Lachaux et al., 1999). When coherence is low, it indicates that across time epochs, the relationship between power in the two signals and/or the relative phase difference between them is inconsistent. Moreover, the coherence measure does not allow specification of whether the relationship between the two signals is stronger in terms of relative phase or power (Lachaux et al., 1999). Coherence can range from zero to one, and it does not 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 this study appear in an earlier report (Ford et al., 2002).

6.2. Methods

Single trial EEG epochs were used from Experiment 1. To translate data from the time domain to the frequency domain, a Fast Fourier Transform (FFT) was calculated on all points. Coherence was calculated for each frequency band of interest (delta: 1–3 Hz; theta: 4–7 Hz; alpha: 8–12 Hz; beta: 13–20 Hz; gamma: 30–50 Hz). Coherence is the spectral cross-correlation between two electrodes normalized by their power spectra (NeuroscanLabs, 1999).

Coherence was calculated between the following electrode pairs displayed in Fig. 6. The coherence values for each electrode pair were averaged across the single trials. The resulting average event-related coherence values for each electrode pair were the dependent variables in the analyses of variance (ANOVA).

6.3. Results

While the ANOVA revealed a main effect of Condition [$F(1,20)=26.28$, $P<0.0001$] indicating greater coherence during talking than listening, the Condition effect interacted with all the other variables resulting in a 6-way interaction [Group×Condition×Hemisphere×Frontal Region×Temporal Site×Frequency Band: $F(6,320)=2.12$, $P<0.05$] which was parsed hierarchically to find a simple main effect of Condition, proceeding only if the highest order interaction was significant in the intermediate ANOVA (from 4-way, to 3-way, to 2-way). A 2-way Group×Condition interaction was significant for theta [$F(1,20)=4.62$, $P<0.05$] over the left hemisphere between lateral frontal (F7) and posterior temporal sites (P3). A similar Group×Condition interaction was significant for delta [$F(1,20)=4.48$, $P<0.05$] over the left hemisphere between lateral frontal (F7) and posterior temporal sites (T5). Finally, at the single factor level, a simple main effect of Condition was observed for controls in both bands [Theta: $F(1,9)=17.17$, $P=0.0025$; Delta: $F(1,9)=5.05$, $P=0.05$], but not for patients [Theta: $F(1,11)=3.28$, $P=0.10$; Delta: $F(1,11)=4.04$, $P=0.07$]. Thus, for controls but not patients, coherence between lateral frontal and posterior temporal sites was greater during Talking than Listening in the theta and delta bands.

Because the effects were stronger for theta than delta, additional analyses focused on this frequency band. The patient group was subdivided into hallucinators (rating of 5, 6 or 7 on the Hallucinatory Behavior item on the BPRS, $n=7$) and non-hallucinators (rating of 1 or 2 on the Hallucinatory Behavior item on the BPRS, $n=5$). We found a significant Condition×Group interaction for theta coherence [$F(2,19)=4.14$, $P=0.03$] in which coherence was greater during Talking than Listening for controls [$F(1,9)=17.17$, $P=0.0025$], tended to be greater for non-hallucinators [$F(1,4)=7.10$, $P=0.056$], but was

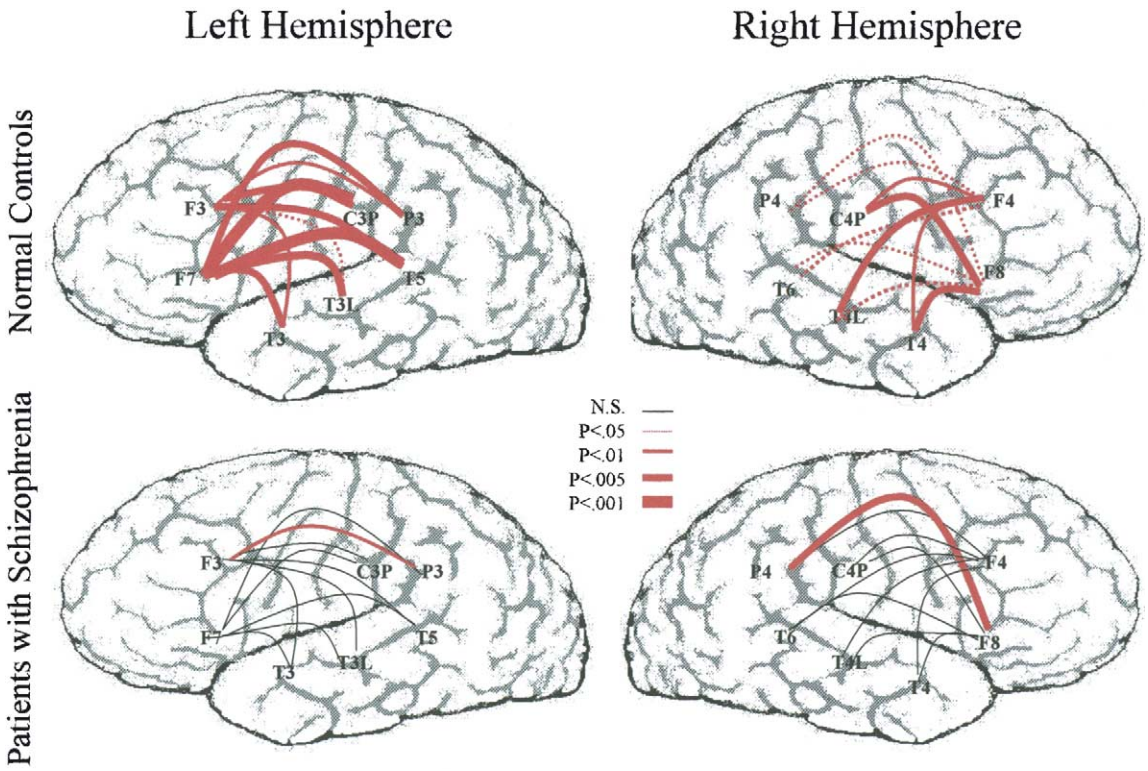

Fig. 6. Experiment 4. Probability levels for *t*-tests showing greater fronto-temporal EEG coherence during talking than during listening superimposed on lateral view of right and left hemispheres for normal controls and patients with schizophrenia. Thicker lines indicate greater coherence during talking than listening. In controls, coherence during talking was greater than during listening for all 20 of the electrode pairs. In patients, this was true for only two of the pairs. Reprinted from Ford et al. (2002) with permission from the Society of Biological Psychiatry.

not for the hallucinators [$F(1,6) = 0.069$, $P = 0.80$]. Thus the failure to increase theta coherence during talking in schizophrenia is primarily observed in the hallucinators.

We compared theta coherence during Talking and Listening for each electrode pair. The resulting t-values and probability levels are portrayed graphically in Fig. 6. In controls, coherence during Talking was greater than during Listening for all 20 of the electrode pairs. In patients, this was true for only two of the pairs.

6.4. Discussion

Using EEG coherence as a measure of functional connection between frontal and temporal brain areas, our results corroborate other functional brain imaging reports of a disconnection between frontal and temporal areas in schizophrenia (e.g., Fletcher et al., 1999, Friston & Frith, 1995, Friston et al., 1995, Norman et al., 1997). The current coherence data are also consistent with the ERP data from Experiments 1, 2, and 3, and augment them by suggesting that there is an interdependence between these areas during talking, that is somewhat disrupted in patients, especially those prone to auditory hallucinations. The greater frontal-temporal coherence during talking than listening in controls may reflect the action of a corollary discharge from frontal brain structures preparing auditory cortex for speech. It is important to note that because of the nature of the coherence statistic, we cannot tell whether high coherences reflect inhibition or excitation. That is, high levels of activation in the frontal speech areas could be related to high levels of excitation or inhibition in the temporal lobes. We do know however that 100 msec before speech is initiated, the spontaneous firing rate of neurons in the middle temporal gyrus diminishes (Creutzfeldt et al., 1989b). Increased coherence during talking implies a continuous dialogue between neural systems responsible for producing speech and those involved in perceiving its effects, and this increase is not seen in patients with schizophrenia in the theta and delta bands. Furthermore, this effect in the theta band was stronger in patients who hallucinated than those who did not. This would suggest that a "break" in the frontal-temporal circuit during the act of overt speech, and perhaps covert speech, is associated with the pathophysiology of auditory verbal hallucinations, possibly because corollary discharge mechanisms normally subserved by this circuitry are compromised. Whether the connection between speech production and speech reception areas is subjectively experienced or whether it is an unconscious automatic signal to the speech reception areas remains an interesting and open question.

7. Summary of Experiments 1, 2, 3, and 4

Data from the first two experiments suggest that the auditory cortex is dampened in responsiveness during talking, confirming the primate (Muller-Preuss & Ploog, 1981) and intra-operative (Creutzfeldt et al., 1989a; Creutzfeldt et al., 1989b) data of others, and extending the MEG data of Curio and colleagues (Curio et al., 2000) to the ERP methodology. In addition, the data from the third experiment suggest that this dampening effect is also seen during inner speech. Data from the fourth experiment suggest that the suppression of the auditory cortex responsiveness is due to a connection between the frontal and temporal lobes. In each, we have shown evidence that normal effects of talking or inner speech do not operate in patients with schizophrenia.

While we have chosen to interpret the data in terms of the action of the corollary discharge mechanism, there are other reasonable competing hypotheses. Among these is the "line busy" hypothesis. According to this view, talking, inner speech, or an on-going internal dialogue, might saturate the auditory cortex, making it unresponsive to external probe stimuli, as if the "line" were "busy." N1 to probes would be reduced if the line were busy or if the corollary discharge was operating, and with these data it is difficult to decide between these two hypotheses. Alternatively, the corollary discharge could be transmitted perfectly well from frontal lobe speech production areas to temporal lobe speech reception areas in patients, but the temporal lobe structures are dysfunctional and relatively unresponsive in schizophrenia, independent of hallucinations. This could be referred to as the "nobody home" hypothesis. Another explanation for our finding is that normal subjects but not patients with schizophrenia may automatically *increase* their auditory sensitivity when they are *not* talking in a manner that can be suppressed by a corollary discharge.

In this paper we present an overview of a series of studies performed to follow up on our initial observations of corollary discharge dysfunction in schizophrenia. The presentation is designed to focus on those results that motivated each successive follow-up study or analysis, rather than reiterate each individual study in full, as these data have already been published. The data presented here, while highlighting a consistent theme, can certainly be subject to different interpretations, as noted above. Furthermore, the studies are all limited by small sample size. Future studies will increase sample size as well as expand the direction of the enquiry. Another limitation of these studies is the limited association detected between actual hallucinatory behavior and electrophysiological indicators of corollary discharge. While significant differences in theta coherence emerged between patients classified as hallucinators and non-hallucinators on the basis of BPRS scores in Experiment 4, efforts to relate N1 measures to scores for recent hallucinatory behavior derived from either BPRS or the SAPS were unsuccessful. This lack of association could be due to the normalizing effects of medication on the symptom but not the mechanism that makes them

possible. Thus N1 measures may reflect the potential for hallucinations rather than their current manifestation. Future studies aim to test larger samples of patients with and without histories of hallucinations and use more comprehensive assessments of this symptom.

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