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Authors

Ford, Judith M
Mathalon, Daniel H
Roach, Brian J
et al.

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Neurophysiological Evidence of Corollary Discharge Function During Vocalization in Psychotic Patients and Their Nonpsychotic First-Degree Relatives

Judith M. Ford*[,1,2], Daniel H. Mathalon[1,2], Brian J. Roach[1], Sarah K. Keedy[3], James L. Reilly[4], Elliot S. Gershon[3], and John A. Sweeney[5]

[1]San Francisco VA Medical Center, San Francisco, CA; [2]Department of Psychiatry, University of California, San Francisco, CA; [3]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL; [4]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL; [5]Departments of Psychiatry and Pediatrics, University of Texas, Southwestern Dallas, TX

*To whom correspondence should be addressed; Psychiatry Service (116D), San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA 94121, US; tel: 415-221-4810, ext. 4187, fax: 415-750-6622, e-mail: Judith.ford@ucsf.edu

Predictions about sensations resulting from motor acts are instantiated through neural mechanisms such as the corollary discharge. With each action, the corollary discharge provides an unconscious comparison between predicted and actual sensations resulting from the action; closer matches result in greater suppression of sensation. This mechanism is disrupted in schizophrenia (SZ) and may contribute to, or reflect a failure to, distinguish self- from externally generated experiences, a hallmark of psychosis. We asked whether disruption is specific to SZ or is seen in other psychotic illnesses and in first-degree relatives of psychotic patients. Corollary discharge function was assessed in SZ patients (n = 30), schizoaffective (SA) patients (n = 19), bipolar patients with a history of psychosis (BPP; n = 39), nonpsychotic relatives of SZ (n = 30), SA (n = 23), and BPP (n = 50) patients, and healthy controls (n = 43). The N1 component of the event-related potential, reflecting auditory cortical responses to sounds, was elicited by speech sound onset as subjects talked and later when they listened to a recording of those sounds. N1 was suppressed during talking compared to N1 during listening, consistent with the suppressive action of the corollary discharge mechanism. Suppression was significantly reduced in SZ and BPP patients, with a similar trend in the smaller SA group. Patient groups did not differ, and unaffected relatives did not differ from controls or probands. The failure to monitor sensations resulting from self-generated actions, implicating corollary discharge dysfunction, may be a common feature across affective and nonaffective psychosis. Data from unaffected family members do not indicate that this is a marker of psychosis risk.

Key words: psychosis/corollary discharge/ERP/N1/first-degree relatives

Introduction

Sensations resulting from our own actions are experienced differently from those coming from external sources. When we move our eyes, we do not perceive a moving room; even ticklish people cannot tickle themselves.[1,2] This suppression of sensation has been attributed to the action of the "efference copy/corollary discharge" system. These terms refer to a corollary, or copy, of the efferent motor command that is sent to appropriate sensory cortex heralding the impending sensation resulting from the action.

Its neurobiology has been elegantly described across the animal kingdom, from nematodes to humans[3]: It allows the cricket to sing without deafening itself; it allows the bat to distinguish its own sonar signals from those produced by other bats.[4] In marmoset monkeys, single-unit activity in the primary auditory cortex is suppressed during vocalization,[5,6] perhaps allowing the monkey both to suppress sensations resulting from its own vocalizations and to tag them as coming from "self."

Similar support for this mechanism during human vocalization comes from single- and multi-unit recordings from the right and left lateral temporal cortices while neurosurgical patients talked and listened to speech.[7,8] During listening to speech, neurons in the superior temporal gyrus responded within 200 ms following speech onset. During overt talking, ongoing activity in approximately one-third of the middle temporal gyrus neurons was suppressed before speech onset.[7]

Noninvasive studies of this mechanism use scalp-recorded electroencephalography (EEG) or magnetoencephalography (MEG) methods in healthy human volunteers. The N1 component of the EEG-based event-related potential (ERP), and the analogous M100

component of the MEG-based field potential, emanate from the primary and secondary auditory cortices, peak about 100 ms after stimulus onset, and index auditory cortical responsiveness. As such, N1[9–14] and M100[15–18] have been used to study the suppressive action of the efference copy/corollary discharge mechanism during vocalization. Consistent with the above invasive studies in human and nonhuman primates, auditory cortical responsiveness in EEG/MEG recordings is reduced during talking compared to that during listening to spoken sounds that are recorded and played back. These findings are consistent with the suppressive action of the efference copy/corollary discharge mechanism.[9–12]

It has been suggested that patients with schizophrenia have a dysfunctional efference copy/corollary discharge mechanism,[19,20] or more generally, a deficit in self-monitoring.[21] Behavioral[22–28] and neurophysiological[9–12,14,29–31] data are consistent with this hypothesis. In several independent samples, we have found that N1 suppression during talking is reduced in patients with schizophrenia compared to healthy controls,[9–12,31] consistent with *dysfunction* of the efference copy/corollary discharge mechanism.

It is unclear whether deficits in this system are specific to schizophrenia or whether they are also seen in other psychotic illnesses. Identifying biological signals related to specific mechanisms associated with psychosis may help clarify the boundaries and overlap between diagnostic entities. Specifically, if a neurobiological marker that is abnormal in schizophrenia is also abnormal in other psychotic illnesses, such as schizoaffective and psychotic bipolar disorders, it would suggest that the marker does not reflect the specific pathophysiology of schizophrenia but rather reflects pathological processes shared by other disorders.

It is also unclear whether deficits in the efference copy/corollary discharge system could serve as an endophenotypic marker of risk for psychosis. In this case, the abnormality should be seen in first-degree relatives unaffected by psychosis. First-degree relatives of people with schizophrenia exhibit many deficits seen in their schizophrenic relatives, but typically to a lesser degree. These deficits might reflect the expression of increased genetic vulnerability to illness.

In this study, our overarching question is whether deficits revealed by our assay of the efference copy/corollary discharge process are specific to the diagnosis of schizophrenia or whether they extend to affective psychotic diagnoses, such as schizoaffective and psychotic bipolar disorders. We predicted that efference copy/corollary discharge deficits would be evident in psychotic patients compared to controls but would be insensitive to diagnostic boundaries within psychosis, being equally evident in schizophrenia, schizoaffective, and psychotic bipolar patients. To test this prediction, we compared healthy controls to each patient group and each patient group to the others.

Our secondary question is whether the efference copy/corollary discharge deficit is present in nonpsychotic first-degree relatives of patients, which would support its role as a potential endophenotype of psychosis and indicate that it may represent a marker of risk for illness. We predicted that failure of N1 suppression would be greater in unaffected relatives than in healthy controls but would be less marked than the failure seen in psychotic probands. To test this prediction, we compared (1) relatives to both probands and controls and (2) each relative group to the others. We also asked whether N1 amplitude (during talking, listening, or N1 suppression) was heritable.

Methods

Subjects

Patients and Healthy Controls. Subject recruitment and data acquisition were completed at the University of Illinois Bipolar & Schizophrenia Network on Intermediate Phenotypes (B-SNIP) site in Chicago. All patients enrolled in the study had a confirmed diagnosis of psychosis. At the time of testing, patients needed to be clinically stable (not in acute exacerbation) and not to have had a medication change in the preceding 4 weeks. Four age- and gender-matched groups were constructed—HC (healthy controls), SZ (schizophrenia patients), SA (schizoaffective patients), and psychotic bipolar disorder patients (BPP)—and are described in table 1.

Patients were recruited from the community and from local community support and advocacy organizations. Only patients with *at least* one first-degree relative willing to participate were enrolled. All subjects completed a Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) of Mental Disorders IV (SCID).[32] Patients were rated on the Positive and Negative Symptom Scale (PANSS),[33] the Young Mania Rating Scale (YMRS),[34] and the Montgomery Asberg Depression Rating Scale (MADRS).[35]

As can be seen in table 1, BPP patients had (1) significantly less severe positive and general symptoms scores than SZ and SA patients and (2) significantly less severe negative symptoms than the SZ patients. SA patients had more current symptoms of mania than either SZ or BPP patients and more symptoms of depression than SZ. There was no difference between patient groups in the chlorpromazine equivalents of their antipsychotic treatment[36] (table 1).

Healthy subjects were required to have no lifetime psychotic or mood disorder and no history of psychotic or bipolar disorders in their first-degree relatives.

Relatives of Patients. Relatives with no history of a psychotic disorder according to SCID criteria are described in table 2. Although the relatives had no history of psychosis, some had other psychiatric diagnoses, which are all listed in table 2.

Table 1. Characteristics of Participants [Mean (SD)]

	Healthy Control (n = 43)	Schizophrenia (n = 30)	Schizoaffective (n = 19)	Bipolar (n = 39)
Demographics				
Age (years)	36.3 (12.3)	34.5 (14.6)	36.6 (13.6)	33.8 (13.1)
Education (years)	14.9 (2.0)[a]	13.3 (2.5)	13.6 (2.8)	14.6 (2.3)
Occupational scale	3.9 (2.0)[a]	5.8 (2.1)	5.2 (2.4)	4.6 (2.2)
Handedness	38 (r), 5 (l)	24 (r), 4 (l), 1 (a)	18 (r), 0 (l), 1(a)	32 (r), 7 (l)
Gender (female)	21	11	12	26
WRAT	102 (15.0)	94.0 (16.8)	101.2 (17.7)	103.6 (15.2)
Total GAF	85.9 (5.8)[a,b,c]	44.3 (8.4)[c,d]	39.5 (5.1)[c,d]	62.1 (12.1)[a,b,d]
Diagnosis (n)	n/a	9 Undifferentiated 12 Paranoid 7 Residual 2 Disorganized	6 Depressive disorder 13 Bipolar — —	n/a
Symptoms measures				
PANSS				
Positive	n/a	19.0 (6.4)[c]	20.3 (4.2)[c]	11.5 (3.3)[a,b]
Negative	n/a	19.1 (6.6)[c]	17.2 (6.6)	14.0 (4.7)[a]
General	n/a	35.1 (8.4)[c]	38.5 (8.7)	30.1 (7.8)[a,b]
Hallucinations	n/a	2.97 (1.7)[b,c]	3.84 (1.5)[a,c]	1.31 (.73)[a,b]
YMRS	n/a	6.4 (5.5)[b]	10.0 (6.0)[a,c]	3.9 (4.0)[b]
MADRS	n/a	8.7 (6.9)[b]	15.6 (11.3)[a]	11.3 (10.3)
Medication				
CPZ equivalents	n/a	494.25	406.34	222.53
Unmedicated	n/a	3	5	8
Atypical antipsychotics	n/a	22	12	30
Typical antipsychotics	n/a	5	3	1

Note: R, right; L, left; A, ambidextrous; WRAT, Wide Range Achievement Test; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Symptom Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; CPZ, chlorpromazine equivalents (mg/day); n/a, not applicable. Due to missing data, the actual sample sizes vary across measures. The actual sample size for education and occupational scale is 38 for healthy controls. The actual sample size for WRAT is 42 for healthy controls. The actual sample size for YMRS is 35 for bipolar patients. The actual sample size for MADRS is 29 for schizophrenia patients and 33 for bipolar patients. The actual sample size for CPZ equivalents is 22 for schizophrenia patients, 16 for schizoaffective patients, and 35 for bipolar patients.
[a]Different from schizophrenia group mean ($P < .05$).
[b]Different from schizoaffective group mean ($P < .05$).
[c]Different from bipolar group mean ($P < .05$).
[d]Different from control group mean ($P < .05$).

All Subjects. All clinical information and diagnoses for each subject were reviewed at a consensus diagnostic meeting. Medical history and Global Assessment of Functioning (GAF; Axis V of DSM-IV) were acquired from all subjects. All subjects were excluded for the presence of medical conditions that impact brain function, head trauma with loss of consciousness >10 min, current substance use ascertained by urine drug screens on the day of testing, and drug abuse in the preceding 3 months or dependence within 6 months according to SCID criteria (DSM-IV).

Procedure

Participants completed the Talk–Listen paradigm, as described previously,[37] using Presentation software (www.neurobs.com/presentation). In the Talk condition, participants were trained to pronounce short (<300 ms), sharp vocalizations of the phoneme "ah" repeatedly in a self-paced manner, about every 1–2 s, for 180 s. The speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through headphones in real time (zero delay). In the Listen condition, the recording from the Talk condition was played back, and participants were instructed simply to listen.

Acoustic Calibration and Standard Stimulus Generation. Participants were coached to produce "ah" vocalizations between 75 and 85 dB by monitoring intensity with a decibel meter held ~6 cm in front of the participant's mouth. Sound intensity was kept the same in Talk and Listen conditions for each participant by ensuring that a 1000-Hz tone (generated by a Quest QC calibrator) produced equivalent decibel intensities when delivered through earphones during the tone's generation (Talk condition) and during its playback (Listen condition). The recorded "ah" vocalizations were digitized and processed offline using an automated algorithm to identify vocalization onset.[37] Trigger codes were inserted into the continuous EEG file at these onsets to allow time-locked epoching and averaging of the EEG data.

Table 2. Characteristics of Relatives [Mean (SD)]

	Schizophrenia Relatives (n = 30)	Schizoaffective Relatives (n = 23)	Bipolar Relatives (n = 50)
Demographics			
Age (years)	41.2 (15.6)	41.4 (15.8)	39.3 (16.3)
Education (years)	14.3 (2.5)	14.6 (2.9)	16.5 (2.4)
Occupational Scale	3.5 (2.0)	3.7 (2.5)	4.0 (2.5)
Handedness	26 (r), 2 (l), 2 (a)	21 (r), 2 (l), 0(a)	43 (r), 6 (l), 1 (a)
Gender (Female)	20	17	32
WRAT	99.0 (15.3)	105.9 (16.3)	104.3 (15.3)
Total GAF	68.9 (14.6)	73.3 (14.6)	74.2 (12.6)
Diagnosis (n)	11 Depressive disorder	13 Depressive disorder	19 Depressive disorder
	1 Panic disorder	3 Alcohol disorder	1 Panic disorder
	3 Alcohol disorder	—	4 Alcohol disorder
	1 Bipolar I	—	5 Bipolar I
	—	—	2 Bipolar II
Medication			
CPZ equivalents	63.30	63.30	126.87
Atypical antipsychotics	2	1	2
Typical antipsychotics	0	0	0

Note: Abbreviations as in table 1. Due to missing data, the range of actual sample sizes across measures is 29–30 for schizophrenia relatives and 47–50 for bipolar relatives.

Data Acquisition and Processing. EEG data were recorded from 64 channels using a Neuroscan Synamps2 system (www.neuroscan.com). Electrodes placed (1) at the outer canthi of both eyes and (2) above and below the right eye were used to record vertical and horizontal electrooculogram (EOG) data. EEG data were continuously digitized at 1000 Hz and referenced to a nose electrode.

After applying a 1-Hz high-pass filter using EEGLAB (http://sccn.ucsd.edu/eeglab/), data were next subjected to fully automated statistical thresholding for EEG artifact rejection (FASTER) using a freely distributed toolbox.[38] The method employs multiple descriptive measures to search for statistical outliers (>±3 SD from mean). This process included 5 steps: (1) outlier channels were identified and replaced with interpolated values in continuous data, (2) outlier epochs were removed from participants' single-trial set, (3) spatial independent components analysis was applied to remaining trials, outlier components were identified (including components that correlated with EOG activity), and data were backprojected without these components, (4) within an epoch, outlier channels were interpolated, and (5) ERP averages for the Talk and Listen conditions were separately assessed in each subject group to identify outlier subjects. Thus, 4 healthy controls, 7 patients, and 7 relatives were excluded from further analysis based on this last step. The final numbers of subjects included in each experiment are given in table 2. Data were re-referenced to averaged mastoid (TP9, TP10) electrodes. Epochs were time-locked to the onset of each "ah" and baseline-corrected 100 ms preceding vocalization. ERP averages were generated using a trimmed means approach, excluding the top and bottom 25% of single-trial values at every data sample in the epoch before averaging to produce a robuster mean estimation.[39] ERPs were then low-pass filtered at 30 Hz.

To address any remaining baseline contamination, a temporal Varimax-rotated principal components analysis was performed on the ERP data.[40] ERPs were reconstructed by excluding factors with a maximum value preceding "ah" onset or that accounted for <0.5% of the variance (46.3% remained). This particular set of processing steps has been used previously on this paradigm with similar effects of Condition (Talk vs Listen).[12]

ERP Analysis. N1 peak amplitude was identified in the ERP as the most negative voltage between 80 and 130 ms after "ah" onset relative to the pre-"ah" baseline (–100 to 0 ms) during both the Talk and Listen conditions.

Statistical Analysis of ERP Effects

Assessment of N1 Suppression. Because physical features of sound, such as intensity and interstimulus interval, affect N1 amplitude, N1 amplitude *suppression* must be estimated by comparing N1s elicited by the identical sequence of sounds during talking and listening. This was done by (1) estimating the Group × Condition (Talk vs Listen) interaction to identify group differences in N1 suppression and (2) calculating a difference score to provide a simple index of N1 suppression (N1 suppression = N1 [Talk] – N1 [Listen]) at each of the 3 frontal–central sites (Fz, FCz, and Cz).

Tests of Primary Hypotheses. N1 peak amplitudes were assessed in a 3-way ANOVA for the between-subjects factor of Group (HC, SZ, SA, and BPP) and the within-subjects factors of Condition (Talk vs Listen) and anterior–posterior (AP) scalp distribution (frontal [Fz], frontal–central [FCz], and central [Cz]). To test our predictions regarding N1 suppression, we contrasted (1) N1 suppression scores in HC to each of the patient groups

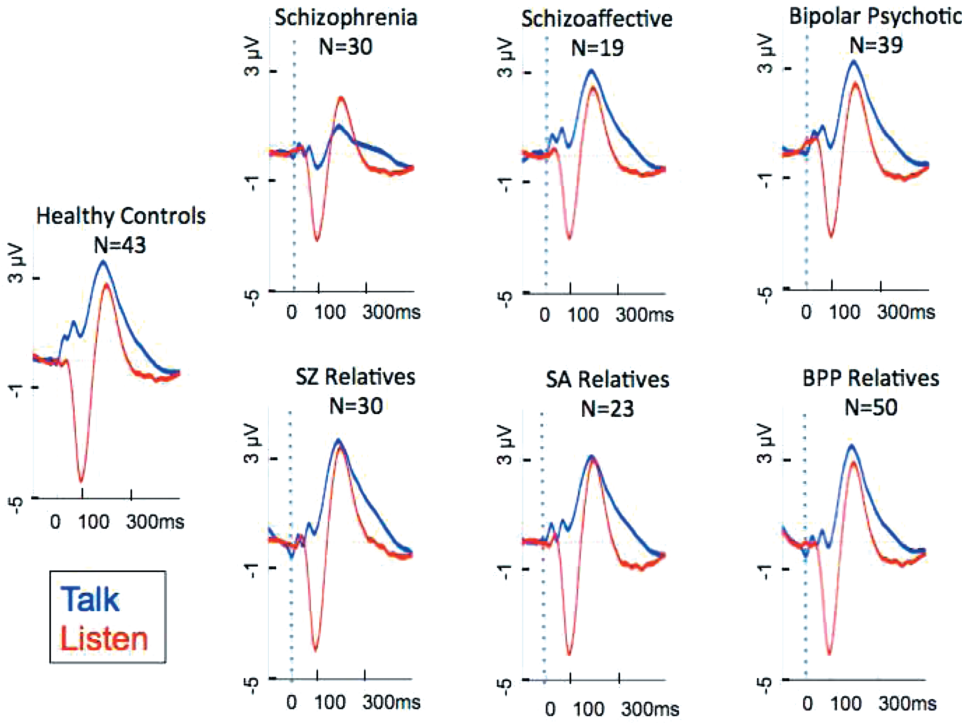

Fig. 1. ERPs elicited by onset of speech sound (0 ms) during Talk and Listen conditions are overlaid for each group at FCz. Voltage in microvolts is on the *y*-axis and time in milliseconds is on the *x*-axis.

and (2) SZ to each of the other groups, using planned comparisons for all follow-up tests. The AP factor was included in the planned comparisons.

Tests of Secondary Hypotheses. In separate analyses using N1 suppression scores, we compared relatives (REL) to both probands and healthy controls. Specifically, we compared: SZREL to SZ and HC; SAREL to SA and HC; and BPPREL to BPP and HC. We also compared each relative group to the others: SZREL vs SAREL; SZREL vs BPPREL; and SAREL vs BPPREL.

Additional Analyses. Because disruptions of the efference copy/corollary discharge mechanism might underlie psychotic experiences, we related N1 suppression at FCz to psychotic symptoms (PANSS positive symptoms, PANSS hallucinations) using Spearman rho correlation tests. Similarly, we related N1 suppression to mania (YMRS) and depression symptoms (MADRS).

To provide a descriptive estimate of the familiality of N1 amplitude during passive listening and during talking, and N1 suppression during talking (N1 [Talk] – N1 [Listen]), at FCz, we used a maximum likelihood method to estimate familiality using SOLAR v4.3.1 linkage analysis software (Southwest Foundation for Biomedical Research, San Antonio, TX).[41] Age and gender were assessed for their significance as covariates. A correction was made to the heritability estimate because families were recruited through the identification of an affected proband and thus were not representative of the general population.[42] It is important to note that the samples are small (SZ families: $n = 30$; SA families: $n = 23$; BPP families: $n = 50$), so h^2 values are reported as preliminary descriptive estimates of the familiality of the measures of interest.

Results

Primary Hypothesis

The grand average ERPs during the Talk and Listen conditions are overlaid in the upper portion of figure 1, separately for each group. As can be seen, N1 was suppressed during Talk compared to Listen in each group, but with an attenuation of this effect in the patient groups.

The results of the ANOVA for N1 peak amplitudes for the factors of Group (HC, SA, BPP, and SZ), Condition (Talk and Listen), and AP (Fz, FCz, and Cz) are shown in table 3. The significant Condition × Group interaction indicated that the Condition effect was different in the different groups as revealed in the planned comparisons. As can be seen in table 4, the N1 suppression effect was greater in HC than in SZ ($P = .004$; effect size = 0.69) and BPP ($P = .02$; effect size = 0.49), with only a trend-level effect in SA ($P = .09$; effect size = 0.45). N1 suppression in SZ was not different from that seen in BPP or SA (table 4). N1 suppression values for each subject, averaged across Fz, FCz, and Cz are plotted in figure 2.

The Condition × Group interaction was also parsed by inspecting the effect of Group during the Talk and Listen conditions separately. The results of the planned

Table 3. ANOVA Results for N1 Amplitude

	df	*F*	Significance
Group	3,127	0.31	0.82
Condition	1,127	105.68	0.000
AP	2,254	6.159	0.01
Condition × Group	3,127	3.369	0.02
AP × Group	6,254	0.978	0.44
Condition × AP	2,254	3.564	0.06
Condition × AP × Group	6,254	0.248	0.96

Note: Group = HC (healthy controls), SZ (schizophrenia patients), SA (schizoaffective patients), and BPP psychotic bipolar disorder patients; Condition = Talk and Listen; AP = Anterior–posterior distribution, namely, Fz, FCz, and Cz.

comparisons can be seen in table 4. N1 during Listening was larger in HC than in SZ, as is often the case,[43] and was also larger in HC than in SA and BPP. There was a trend (P = .10) for N1 during Talking to be *larger* in SZ than in HC, as we have reported previously.[10]

Secondary Hypothesis

The grand average ERPs during the Talk and Listen conditions are overlaid in the lower portion of figure 1, separately for each group of relatives. Individual scores for N1 suppression are plotted in figure 2. The results of the analyses comparing relatives to healthy controls and probands are shown in table 5. None of the groups of relatives differed from the control group, from the proband groups, or from each other.

Other Analyses

N1 suppression failure was not related to symptoms (PANSS positive, PANSS hallucinations, YMRS, or MADRS) in any of the 3 patient groups (Ps = .11 to .89).

For N1 suppression, N1 during talking, and N1 during listening, we estimated familiality separately within each diagnostic group and also collapsed across groups to achieve greater power. Consistent with the results of Turetsky et al.,[44] there is evidence for familiality of N1 during passive listening in SZ relatives (n = 35, h^2 = 0.56, P = .04, with age and gender as significant covariates), BPP relatives (n = 43, h^2 = 0.68, P = .04, with age as a significant covariate), and in the larger group (n = 97, h^2 = 0.57, P = .01, with age as a significant covariate), but not in SA relatives (n = 19, h^2 = 0.32, P = .13, with age and gender as significant covariates). There is trend-level evidence for familiality of N1 suppression in the larger group (n = 97, h^2 = 0.33, P = .09), but not for N1 during talking, either in the larger group or when broken down into separate diagnostic groups.

Discussion

We confirmed our previous findings of reduced N1 during talking compared to N1 during listening in chronic patients with schizophrenia.[9–11,31] These findings suggest that patients with schizophrenia have a dysfunction in the cortical suppression of the processing of self-initiated speech sounds and, thus, in the efference copy/corollary discharge mechanism.

Across the animal kingdom, the efference copy/corollary discharge mechanism allows an animal to unconsciously monitor its own motor output in order to correct it "on the fly," to suppress sensations resulting from movement, and to disambiguate, or "tag," the source of the sensation. Evidence of this mechanism will vary depending on the environmental niche a species occupies and the action being executed. We suggest that imprecision[31] or delay[45,46] in "tagging" the source of the sensation during vocalization may underpin psychotic experiences, whereas failure to correct actions in the moment may result in motor awkwardness,[30] both of which are features of schizophrenia.

Because of its presumed role in psychosis, we predicted that dysfunctional efference copy/corollary discharge would extend to other psychotic illnesses, namely bipolar and schizoaffective diseases. We partially confirmed this hypothesis: psychotic bipolar patients had significantly reduced N1 suppression, but SA patients only tended to have abnormal suppression (P = .09). The nonsignificant effect in the SA patients in part reflects the small sample (n = 19), as the effect sizes for SA and BPP groups were similar (0.45 vs 0.49).

N1 suppression failure is probably *not* due to current psychotic symptoms: N1 suppression failure did not correlate with positive symptoms or hallucinations; and although the groups differed in current severity of these symptoms, they

Table 4. Simple Patient-Group Contrasts for N1 Amplitude

N1 Talk–N1 Listen			N1 Talk			N1 Listen		
Effect	Significance	Cohen's *d*	Effect	Significance	Cohen's *d*	Effect	Significance	Cohen's *d*
HC > SZ	0.004	0.69	SZ > HC	0.10	0.39	HC > SZ	0.02	0.59
HC = SA	0.09	0.45	HC = SA	0.61	0.13	HC > SA	0.03	0.66
HC > BPP	0.02	0.49	HC = BPP	0.42	0.16	HC > BPP	0.007	0.60
SZ = SA	0.45	0.24	SZ = SA	0.40	0.30	SZ = SA	0.93	0.03
SZ = BPP	0.44	0.20	SZ = BPP	0.38	0.24	SZ = BPP	0.91	0.03

Note: Abbreviations as in table 3.

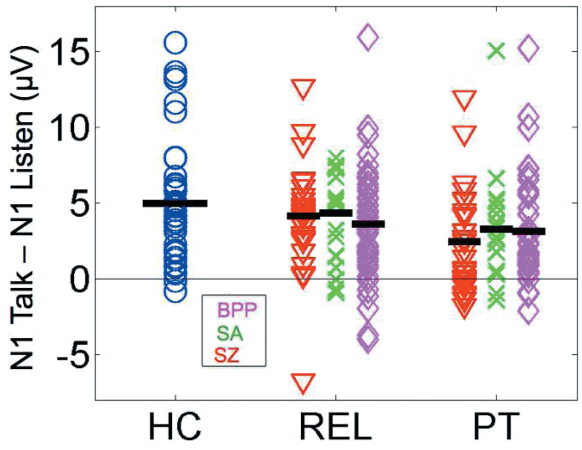

Fig. 2. Individual subject N1 suppression scores averaged over Fz, FCz, and Cz electrodes for each of the groups: healthy controls (HC), relatives (REL), and patients (PT). Data from patients and relatives are further segregated by diagnosis of the patient or proband, in the case of the relatives: schizophrenia (SZ), schizoaffective (SA), and psychotic bipolar (BPP). Group means are indicated with thick horizontal lines.

Table 5. Simple Relative-Group Contrasts for N1 Amplitude (Talk–Listen)

Comparison	Significance	Cohen's *d*
Relatives vs controls		
SZREL = HC	0.34	0.22
SAREL = HC	0.49	0.18
BPPREL = HC	0.08	0.36
Relatives vs probands		
SZREL = SZ	0.07	0.52
SAREL = SA	0.36	0.32
BPPREL = BPP	0.35	0.14
Relatives vs relatives		
SZREL = SAREL	0.88	0.05
SAREL = BPPREL	0.42	0.20
SZREL = BPPREL	0.50	0.15

Note: Abbreviations as in table 3. SZREL, SAREL, and BPPREL, relatives of SZ, SA, and BPP, respectively.

did not differ in N1 suppression. In other words, at least within relatively stabilized patients, N1 suppression during talking does not appear to be related to current clinical state. This suggests that a deficit in corollary discharge is a persistent feature in patients with a history of psychosis. Whether N1 suppression is more impaired in acutely psychotic patients remains a question for future research.

A secondary aim of this study was to assess whether reduced N1 suppression during talking was a possible endophenotype of schizophrenia, specifically, and psychosis, more generally. Our hypothesis was that unaffected relatives of psychotic patients would have significantly less N1 suppression than controls and more than probands. However, we found no support for this. The relatives of the BPP, SA, and SZ patients all showed similar effects; the suppression was not reduced relative to controls but neither was it different from that of the probands. The effect sizes for comparisons between relatives and controls were small, suggesting weak or null effects. N1 suppression was also not significantly heritable, but there was a trend for heritability. Thus, the data from this study do not support the hypothesis that N1 suppression failure is a robust endophenotype for psychosis risk. It remains possible that we failed to detect an effect due to limited liability within the relative group because we excluded relatives who were affected by psychosis, included relatives beyond the age of risk, or because of potential ascertainment bias related to decisions of study-eligible family members invited to participate[AU: Please check the insertion of "invited" in the sentence "It remains possible that we failed to.."].

Thus, although we have strong evidence that a deficit in the efference copy/corollary discharge mechanism exists in patients with the 3 target psychotic disorders, the absence of significant impairment in unaffected relatives fails to indicate that this alteration is an endophenotype for psychosis *risk*. However, although the number of families going into the heritability analysis was small, we do have trend-level evidence that N1 suppression is heritable across psychosis kinship groups. Furthermore, N1 during passive listening demonstrated significant familiality across kinship groups and within the SZ and BPP groups, with effect levels consistent with findings from the Consortium on the Genetics of Schizophrenia (COGS).[44]

Although our findings confirm the relative failure of N1 suppression in schizophrenia that we have described previously, it differs in one respect. Contrary to our other reports with this[9,12] and similar[10,11,31] paradigms, SZ patients in the present study did show significant suppression of N1 during talking compared to that during listening, although it was less pronounced than the suppression seen in controls. Possibly this group of patients was less severely affected by their illness.

In summary, efference copy/corollary discharge dysfunction, as reflected in failures of N1 suppression during talking extends beyond schizophrenia and affects other psychotic disorders. It may reflect a more general alteration across psychotic disorders, and it may reflect the trait rather than the state of psychosis. The data from the present study do not suggest that it reflects a risk phenotype, nor do they suggest that it is robustly heritable in families with a psychotic proband.

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