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Author for correspondence:
Judith M. Ford, E-mail: Judith.ford@ucsf.edu

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Deficient auditory predictive coding during vocalization in the psychosis risk syndrome and in early illness schizophrenia: the final expanded sample

Daniel H Mathalon[1,2], Brian J Roach[1,2], Jamie M Ferri[1], Rachel L Loewy[1], Barbara K Stuart[1], Veronica B Perez[3,4], Tara H Trujillo[1,2] and Judith M Ford[1,2]

[1]University of California, San Francisco (UCSF), San Francisco, CA, USA; [2]Veterans Affairs San Francisco Healthcare System, San Francisco, CA 94121, USA; [3]California School of Professional Psychology (CSPP), Alliant International University, San Diego, CA, USA and [4]University of California, San Diego (UCSD), La Jolla, CA, USA

Abstract

Background. During vocalization, efference copy/corollary discharge mechanisms suppress the auditory cortical response to self-generated sounds. Previously, we found attenuated vocalization-related auditory cortical suppression in psychosis and a similar trend in the psychosis risk syndrome. Here, we report data from the final sample of early illness schizophrenia patients (ESZ), individuals at clinical high risk for psychosis (CHR), and healthy controls (HC).

Methods. Event-related potentials (ERP) were recorded from ESZ ($n = 84$), CHR ($n = 71$), and HC ($n = 103$) participants during a vocalization paradigm. The N1 ERP component was elicited during production (Talk) and playback (Listen) of vocalization. Age effects on N1 suppression (Talk–Listen), Talk N1, and Listen N1 were compared across groups. N1 measures were adjusted for normal aging before testing for group differences.

Results. Both ESZ and CHR groups showed reduced Talk–Listen N1 suppression relative to HC, but did not differ from each other. Listen N1 was reduced in ESZ, but not in CHR, relative to HC. Deficient Talk–Listen N1 suppression was associated with greater unusual thought content in CHR individuals. N1 suppression increased with age in HC (12–36 years), and while CHR individuals showed a similar age-related increase, no such relationship was evident in ESZ.

Conclusions. Putative efference copy/corollary discharge-mediated auditory cortical suppression during vocalization is deficient in ESZ and precedes psychosis onset, particularly in CHR individuals with greater unusual thought content. Furthermore, this suppression increases from adolescence through early adulthood, likely reflecting the effects of normal brain maturation. This maturation effect is disrupted in ESZ, presumably due to countervailing illness effects.

During talking, our brains automatically generate predictions about the sound of our impending vocalizations in order to adjust ongoing speech to better match our intentions (Burnett *et al.*, 1998; Houde and Jordan, 1998; Sitek *et al.*, 2013) and to mirror our social environment (Pardo, 2006). At a more fundamental level, our brains may use these predictions to distinguish auditory sensations resulting from our own actions, including overt actions (e.g. speech) and possibly covert actions (e.g. thoughts), from externally generated sounds (Crapse and Sommer, 2008; Greenlee *et al.*, 2011). Individuals with schizophrenia, however, appear to have difficulties predicting the sensory consequences of their own actions (Ford and Mathalon, 2012). Indeed, deficiencies in generating predictions about the sensations resulting from thoughts and inner speech, and a consequent failure to experience them as self-generated, have been posited to underlie psychotic symptoms including auditory hallucinations and the loss of a normal sense of agency (e.g. delusions of alien control) in schizophrenia (Feinberg, 1978; Feinberg and Guazzelli, 1999).

An action-based predictive coding mechanism has been theorized to underlie our ability to anticipate the sensory consequences of our actions, detect mismatches between expected and observed sensations, and appropriately adjust future actions, in a largely unconscious and automatic fashion (Crapse and Sommer, 2008; Houde and Nagarajan, 2011). This mechanism is posited to involve transmission of an 'efference copy' of a motor command to relevant regions of sensory cortex where it produces a 'corollary discharge' representing the anticipated sensory consequences of the motor action (Von Holst and Mittelstaedt, 1950). The efference copy/corollary discharge mechanism is ubiquitous and has been demonstrated in visual, sensorimotor and auditory systems across a range of species (Crapse and Sommer, 2008) from crickets (Poulet and Hedwig, 2002), to primates (Eliades and Wang, 2003). In the auditory

domain, regions subserving vocalization in the frontal lobes send motor commands via efferent motor pathways to muscle groups to produce the intended sound. Simultaneously, these frontal vocalization regions are posited to send an efference copy of the motor commands to auditory cortex, giving rise to a corollary discharge representing the predicted sound. When the corollary discharge matches the actual auditory consequence of the vocalization, the auditory cortical response to the generated speech sound is attenuated, and the match between intended and executed speech is unconsciously recognized (Houde and Jordan, 2002; Eliades and Wang, 2003, 2005). In this way, suppression of auditory cortex during speech may function not only to identify speech production errors, but also to tag vocalizations as self-generated, distinguishing them from externally generated sounds (Feinberg, 1978; Seal *et al.*, 2004).

The function of efference copy/corollary discharge mechanisms has been inferred through studies demonstrating reduced auditory cortical responses to self-generated compared with externally generated sounds. For example, the N100 (N1) component of the auditory event-related potential (ERP) elicited by sounds, and its counterpart in magnetoencephalographic recordings (M100), are reduced in amplitude in response to vocalizations as they are produced relative to when they are played back (Curio *et al.*, 2000; Ford *et al.*, 2001; Houde *et al.*, 2002; Heinks-Maldonado *et al.*, 2005, 2006, 2007; Ford *et al.*, 2007*a*, 2007*b*; Chen *et al.*, 2011; Greenlee *et al.*, 2011; Ford *et al.*, 2013; Sitek *et al.*, 2013; Wang *et al.*, 2014). This putative corollary discharge mechanism is present by adolescence, but it is unclear whether it is fully developed or continues to develop from adolescence through early adulthood as the brain matures (Perez *et al.*, 2012).

In patients with schizophrenia, abnormal efference copy/corollary discharge mechanisms have been hypothesized to underlie impairments in the ability to make predictions about the sensory consequences of self-generated behaviors, including covert behaviors such as thinking/inner speech (Brebion *et al.*, 2000; Frith *et al.*, 2000; Lindner *et al.*, 2005), and have been proposed as potential mechanisms underlying delusional thinking and misperceptions associated with psychosis (Feinberg, 1978; Feinberg and Guazzelli, 1999; Blakemore *et al.*, 2000; Ford and Mathalon, 2005). Unusual thought content and disorganized communication differentiated between clinically high risk (CHR) individuals who transitioned to psychosis and those who did not (Addington *et al.*, 2015). ERP studies have demonstrated that patients with schizophrenia show less suppression of the auditory N1 in response to self-generated vocalization than healthy controls (HCs) (Ford *et al.*, 2001, 2007*b*; Mathalon and Ford, 2008; Perez *et al.*, 2012). Reduced suppression of auditory responses to vocalization extends to psychosis more generally and has been reported in patients with psychotic bipolar disorder and schizoaffective disease (Ford *et al.*, 2013). We have also reported similar abnormalities in schizophrenia patients early in their disease course (Perez *et al.*, 2012), suggesting they are not due to chronicity related clinical sequelae of the illness such as cumulative medication exposure and long-standing social and occupational dysfunction. Additionally, patients with schizophrenia do not display expected suppression of N1 in response to unaltered speech relative to real-time pitch-altered speech, as is seen in HCs (Heinks-Maldonado *et al.*, 2007). Together these findings suggest that patients with schizophrenia show attenuated or absent suppression of auditory cortex in response to self-generated sounds, possibly due to deficits in efference copy/corollary discharge mechanisms. These deficits, consequently, may underlie an inability to make predictions about the sensory consequences of self-generated actions and to utilize them to adjust behavior and tag experiences as self-generated.

Goals of this study

With the emergence of validated clinical criteria for identifying individuals at high risk for developing psychosis (Phillips *et al.*, 2000; Miller *et al.*, 2002, 2003; Cannon *et al.*, 2008; Yung, 2008; Woods *et al.*, 2009), research efforts have focused on examining whether neurobiological abnormalities present in schizophrenia are also evident during the clinical prodrome preceding the onset of psychosis. Previously, we reported that individuals at CHR for psychosis had N1 suppression values that were intermediate between healthy comparison (HC) subjects and patients with schizophrenia who were relatively early in their illness course (ESZ); however, the CHR group was not statistically distinguishable from either HC or ESZ (Perez *et al.*, 2012). Our primary aim in this paper was to analyze the final sample collected in this project to achieve a better estimate of the true effect.

Based on our earlier findings, we predicted that CHR and ESZ would both have diminished speech-related N1 suppression, similar to our prior observations in chronic patients (Ford *et al.*, 2001, 2007*a*, 2007*b*, 2013; Heinks-Maldonado *et al.*, 2007). We further predicted that abnormalities would be greater in CHR subjects who later converted to a psychotic diagnosis. To test this, we compared CHR subjects who converted to psychosis with those who did not after 12 months of follow-up. A secondary aim, based on Feinberg's initial proposal (Feinberg, 1978), was to examine whether abnormalities in the corollary discharge mechanism in ESZ and CHR individuals would be related to the severity of their unusual thought content. Thus, we predicted that ESZ and CHR would show a relationship between deficient N1 suppression during speech, a putative reflection of corollary discharge dysfunction, and the severity of unusual thought content. This was tested with clinical symptom ratings in the CHR and ESZ groups. Finally, because our sample of HC spanned a wide age range, we asked if age affected speech-related N1 suppression and whether the normal age relationship was altered in the ESZ and CHR samples.

Method

Participants

Study participants included 71 individuals at CHR for psychosis, 84 patients with ESZ, and 103 HC subjects. See Table 1 for demographic and clinical data.

CHR participants were recruited from the University of California, San Francisco's (UCSF) Prodromal Assessment, Research, and Treatment Clinic. CHR patients met Criteria of Prodromal Syndromes (COPS) based on the Structured Interview for Prodromal Syndromes (SIPS) (Miller *et al.*, 2002, 2003). COPS criteria comprise three non-mutually exclusive subsyndromes: (i) attenuated psychotic symptoms ($n = 69/71$), (ii) brief intermittent psychotic states ($n = 0/71$), and (iii) genetic risk with deterioration in social/occupational functioning ($n = 7/71$).

ESZ patients within 5 years of illness onset (1.85 ± 1.43 years) were recruited from the Early Psychosis Clinic at UCSF and the community. Diagnosis of schizophrenia or schizoaffective disorder was confirmed using the Structured Clinical Interview for DSM-IV (SCID) (First *et al.*, 2002). ESZ had no DSM-IV substance dependence in the past year.

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Table 1. Group demographic data[a]

	ESZ	CHR	HCs	Between-group comparison (p value)
Number of participants	84	71	103	
Age (years)	21.9 (4.1) (14–35)	19.4 (4.7) (12–32)	22.6 (6.3) (12–35)	<0.001
Gender	23F, 61M	30F, 41M	42F, 61M	0.09
Average parental SES[b]	33.3 (15.6)	35.4 (16.1)	30.7 (13.8)	0.12
Handedness[c]	77R, 3L, 4A	59R, 7L, 5A	94R, 8L, 1A	0.16
Estimated IQ[d]	104.5 (9.67)	104.9 (11.66)	109.1 (8.72)	0.002
Antipsychotic medication class	9U, 70A, 2T, 3A + T	58U, 13A	103U	
SANS global attention	2.29 (1.22)			
SANS anhedonia	2.63 (1.18)			
SANS alogia	1.09 (1.37)			
SANS avolition	2.31 (1.41)			
SANS affective flattening	1.75 (1.51)			
SAPS hallucinations	1.35 (1.67)			
SAPS delusions	1.79 (1.52)			
SAPS thought disorder	0.75 (1.11)			
SAPS bizarre behavior	0.5 (0.84)			
SOPS unusual thought content		2.83 (1.57)		
SOPS suspiciousness		2.16 (1.62)		
SOPS grandiosity		1.00 (1.48)		
SOPS hallucinations		2.23 (1.58)		
SOPS disorganization		1.42 (1.49)		

U, unmedicated; A, atypical antipsychotic; T, typical antipsychotic; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SOPS, Scale of Prodromal Symptoms.

[a]Values are given as number gender, handedness, CHR criteria, and antipsychotic type. Group means with the standard deviation for age, parental socioeconomic status, intelligence quotient, PANSS, and SOPS are reported. Gender and handedness were analyzed with Pearson χ^2 tests. Age, parental socioeconomic status, and intelligence quotient were analyzed with one-way ANOVA.

[b]The Hollingshead (1975) four-factor index of parental socioeconomic status (SES) is based on a composite of maternal education, paternal education, maternal occupational status, and paternal occupational status. Lower scores represent higher SES. SES values are missing from one schizophrenia patient.

[c]The Crovitz-Zener (1962) questionnaire was used to measure handedness and categorize as right (R), left (L), or ambidextrous (A).

[d]The Wechsler Adult Intelligence Scale (WAIS-III) full-scale intelligence quotient (FSIQ) was estimated based on the Wechsler Test of Adult Reading (WTAR) for native English-speaking subjects who were 16 years of age or older at testing (N = 219) or Wechsler Abbreviated Scale of Intelligence (WAIS-II) two-subtest (Vocabulary and Matrix Reasoning) T scores for all other subjects (N = 32). Estimated IQ values are missing from four HC subjects and three CHR patients.

HC participants were recruited from the community and did not meet criteria for any Axis I diagnosis based on the SCID, or for participants 16 years of age, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (Kaufman *et al.*, 1997). HC had no history of substance abuse within the past year based on a SCID interview and no first-degree relative with a psychotic disorder.

Exclusion criteria for all groups included estimated intelligence quotient <70, a history of significant medical or neurological illness, or a history of head injury resulting in loss of consciousness. The study was approved by the institutional review board of UCSF, and adult participants provided written informed consent. In the case of minors, parents provided written informed consent and minors provided written informed assent. All interviews were conducted by trained interviewers, including a clinical psychologist, clinical psychology pre-doctoral intern, clinical social worker, or research assistant.

Clinical ratings

For the ESZ sample, a clinically trained research assistant, psychiatrist, or clinical psychologist rated symptoms using the SAPS (Andreasen, 1984). Symptom interviews were typically done within 1 week of ERP testing, ranging from 64 days to the same day (M = 8.1, S.D. = 8.7 days). For the CHR sample, prodromal symptoms were rated using the Scale of Prodromal Symptoms (SOPS) administered as part of the SIPS interview (Miller *et al.*, 2002, 2003). Symptom ratings were less proximal to ERP testing in the CHR sample, ranging from 170 days to the same day (M = 23.6, S.D. = 25.5 days).

Procedure

Participants completed the Talk–Listen paradigm, as described previously (Ford *et al.*, 2010), using Presentation software (http://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 187 s. The speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through Etymotic ER3-A insert earphones in real-time (zero delay). In the Listen condition, the recording from the Talk condition was played back, and

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participants were instructed simply to listen. The number of ahs generated for both Talk and Listen conditions by ESZ, CHR, and HC groups was not significantly different.

Data acquisition and pre-processing

Electroencephalogram (EEG) data were recorded from 64 channels using a BioSemi ActiveTwo system (http://www.biosemi.com). Electrodes placed at the outer canthi of both eyes, and above and below the right eye, were used to record vertical and horizontal electro-oculogram data. EEG data were continuously digitized at 1024 Hz and referenced offline to averaged earlobe electrodes before applying a 1 Hz high-pass filter using EEGlab (Delorme and Makeig, 2004). Data were next subjected to Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) using a freely distributed toolbox (Nolan *et al.*, 2010). The method employs multiple descriptive measures to search for statistical outliers (>±3 S.D. from mean). This process included five 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 electrooculography (EOG) activity], and data were back-projected without these components, (4) within an epoch, outlier channels were removed and interpolated, and (5) ERP averages for the Talk and Listen conditions were subtracted and difference waveforms were separately assessed in each subject group to identify outlier subjects. Unlike our previous report (Perez *et al.*, 2012), the FASTER processing approach was modified here between steps 2 and 3 to include canonical correlation analysis (CCA). CCA was used as a blind source separation technique to remove broadband or electromyographic noise from single trial EEG data, generating de-noised EEG epochs. Our approach is similar to the CCA method described by others (De Clercq *et al.*, 2006; Ries *et al.*, 2013), with some important differences (see online Supplementary Methods).

Epochs were time-locked to the onset of each 'ah' and baseline corrected using the −100 to 0 ms baseline preceding vocalization. ERP averages were generated using a trimmed means approach, excluding the top and bottom 5% of single trial values at every data sample in the epoch before averaging to produce a more robust mean estimation (Leonowicz *et al.*, 2005).

To remove any remaining baseline contamination by speech-related artifacts, a temporal pro-max-rotated principal components analysis (PCA) was performed on the ERP data (Sinai and Pratt, 2002; Kayser and Tenke, 2003). ERPs were reconstructed after excluding factors that had a maximum loading during the temporal baseline window preceding 'ah' onset or that accounted for <0.3% of the variance. N1 was identified in the ERP as the most negative peak between 60 and 140 ms 'ah' onset. The N1 Talk–Listen suppression effect was estimated using the N1 peak amplitude Talk–Listen difference score at Cz, following the method we used in our prior report (Perez *et al.*, 2012).

Statistical correction for normal aging effects

To control for the effects of normal brain maturation and aging, N1 amplitude Talk–Listen difference scores at Cz were regressed on age in the HC group, and the resulting regression equation was used to calculate age-corrected N1 Talk–Listen difference *z*-scores for all groups, including CHR and ESZ groups. This was done by subtracting the predicted N1 Talk–Listen difference score based on a subject's age from his/her observed difference score, and then dividing by the standard error of regression associated with the age-regression model run in HC. The resulting age-corrected *z*-scores reflect deviations from the value expected for a healthy individual at a specific age. This method has been used previously (Perez *et al.*, 2012), and it is preferable to using age as a covariate in an analysis of covariance (ANCOVA) model because it only removes normal aging effects whereas ANCOVA tends to also remove pathological aging effects from the patient data. We also assessed N1 to vocalizations from the Talk and Listen conditions separately, after removing any effects of normal aging using the method just described.

Statistical analysis

Group differences for age-adjusted *z*-scores representing Talk–Listen N1 amplitude suppression, Talk N1 amplitude, and Listen N1 amplitude were assessed using analysis of variance (ANOVA). Pair-wise group differences were assessed using least squares differences (LSD) *post-hoc* tests, which controls for type I errors in the special case of three groups (Howell, 2017). To assess for differences in the relationship between N1 suppression and age among the three groups, we used a general linear model with age, group, and group × age as regressors. In this model, the group × age interaction tests for group differences in the slopes of the age relationships.

Although our focus was on Unusual Thought Content and Delusions, we assessed the relationship between symptom severity and the age-adjusted *z*-scores representing Talk–Listen N1 suppression for all five positive symptom items from the SOPS in the CHR sample (P1: Unusual Thought Content; P2: Suspiciousness; P3: Grandiose Ideas; P4: Perceptual Abnormalities/Hallucinations; P5: Disorganized Communication) and all four global items from the SAPS in the ESZ sample (Hallucinations, Delusions, Thought Disorder, and Bizarre Behavior). The significance levels were Bonferroni corrected to $p = 0.01$ for the CHR sample, and $p = 0.0125$ for the ESZ sample.

Results

Group differences in speech-related N1 suppression

The grand average ERP waveforms at Cz, showing N1 for Talk and Listen conditions in each group, are presented in Fig. 1. Inspection of these waveforms reveals the expected N1 suppression during Talk compared with Listen. Mean N1 amplitudes at Cz for the Talk and Listen conditions are plotted in Fig. 2, where we also show the N1 suppression effect after *z*-scoring to remove the effects of normal aging. In Table 2, we show the results of the one-way ANOVA of the *z*-scored N1 suppression values, and the follow-up tests. There was a significant main effect of group due to HC having greater N1 suppression than CHR and ESZ, who did not differ from each other.

Group differences in N1 during talk and listen conditions

The means and waveforms suggest that the attenuated suppression effects in ESZ compared with HC was due to larger N1s during Listen in the HC. This was confirmed by ANOVA of the N1 values during the Listen condition (Table 2). The data shown in

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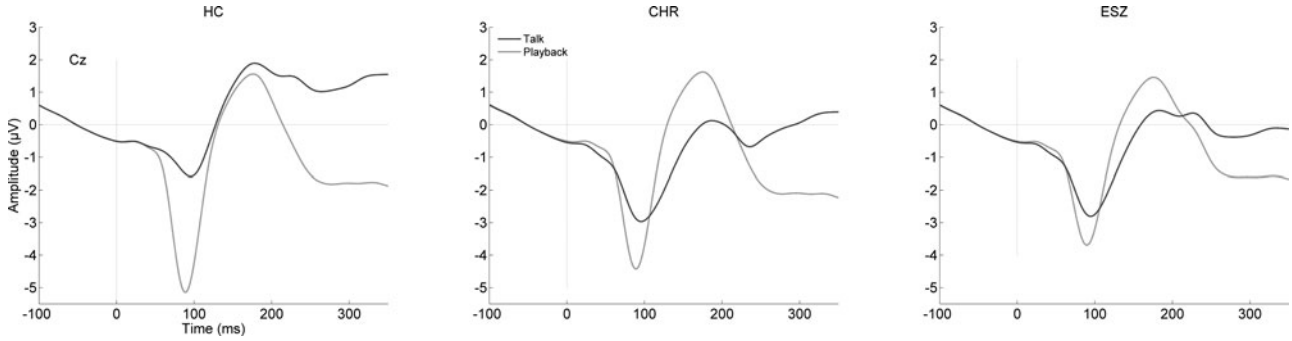

Fig. 1. ERP waveforms for Talk and Listen conditions show the N1 component during the Talk (blue) and Listen (red) conditions recorded at Cz. The N1 amplitude during Talk is reduced relative to Listen in HC (left). This effect is attenuated in the CHR patients (middle) and ESZ patients (right).

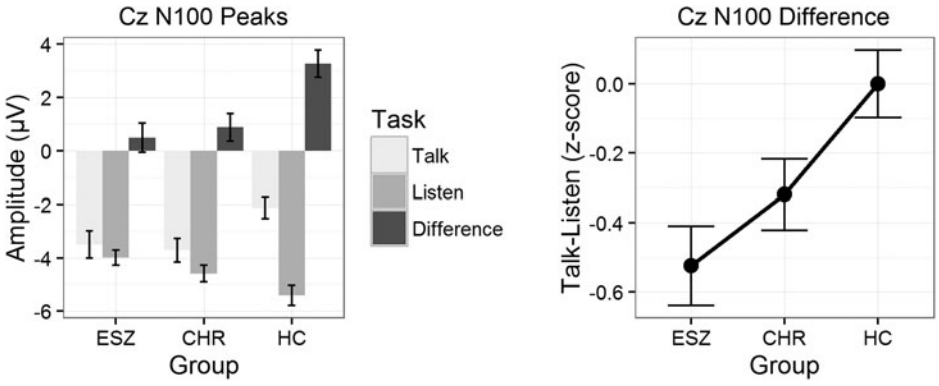

Fig. 2. (Left) Bar graphs show group means and standard errors for N1 amplitude at Cz assessed during Talk and Listen conditions. Normal speech-related N1 suppression is shown in HC (left; Talk: $M = -2.14$, S.E. = 0.393; Listen: $M = -5.42$, S.E. = 0.379), while there is reduced N1 suppression in ESZ patients (left; Talk: $M = -3.38$, S.E. = 0.497; Listen: $M = -3.97$, S.E. = 0.285). CHR patients (middle; Talk: $M = -3.71$, S.E. = 0.446; Listen: $M = -4.59$, S.E. = 0.312) show an effect that is similar to the ESZ. All amplitude values are given in microvolts (μV). (Right) Line graph shows mean N1 Talk–Listen difference scores at Cz (in μV) for the HC group, CHR, and ESZ patients. Age-correction was done using the HC group, causing their group average to be equal to zero, while negative suppression *z*-scores in CHR and ESZ reflect reduced suppression in these groups, accounting for normal aging effects in N1 suppression.

Table 2. Group analyses for speech-related N1 amplitudes at Cz for suppression (top), during Talk (middle), and Listen (bottom)

	ANOVA				Pair-wise comparisons			
	df	Mean square	*F*	Sig.	Group comparison	Mean difference	*t* value	Sig.
N1 peak suppression (Talk–Listen) *z*-scored values at Cz								
Group	2	6.54	6.83	0.001*	HC *v.* CHR	−0.32	−2.11	0.036*
Error	255	0.98			HC *v.* ESZ	−0.53	−3.65	0.0003*
Total	257				CHR *v.* ESZ	−0.21	−1.31	0.43
N1 peak amplitude at Talk *z*-scored values at Cz								
Group	2	2.76	2.28	0.1046	HC *v.* CHR	−0.25	−1.49	0.14
Error	255	1.10			HC *v.* ESZ	−0.33	−2.02	0.04*
Total	257				CHR *v.* ESZ	−0.07	−0.42	0.67
N1 peak amplitude during Listen *z*-scored values at Cz								
Group	2	3.12	4.54	0.01156*	HC *v.* CHR	0.17	1.33	0.18
Error	255	0.83			HC *v.* ESZ	0.37	3.01	0.003*
Total	257				CHR *v.* ESZ	0.20	1.47	0.14

*Significance based on $\alpha = 0.05$, two-tailed.

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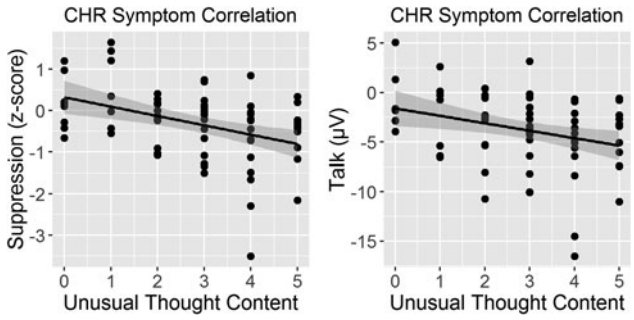

Fig. 3. Scores from SOPS Unusual Thought Content item are plotted against N1 amplitude suppression *z*-scores at Cz (left) and N1 amplitude at Cz (in μV) during Talk (right) for the CHR sample.

Figs 1 and 2 also suggest that the attenuation in the CHR group was due to both larger N1s during Talk and smaller N1s during Listen than seen in the HC; however, the group (CHR *v.* HC) comparison was not significant for either single condition (Table 2).

Converter v. non-converter differences in N1 suppression

CHR individuals who converted to a psychotic disorder (converters $n = 8$) were compared with CHR non-converters ($n = 37$) who had been followed clinically for at least 12 months. The converters did not have significantly less N1 suppression than the non-converters followed for 12 months ($p = 0.73$). Converters had larger N1s during Talk than non-converters, but this was not significant ($p = 0.158$). Finally, N1 during Listen was not affected by converter status ($p = 0.364$).

Correlational analyses with clinical ratings

In the CHR group, unusual thought content was correlated with age-corrected suppression of N1 during Talk compared with Listen ($r = -0.404$, $p < 0.001$) such that subjects with more unusual thought content showed less N1 suppression. This is shown in the scatterplots of Fig. 3. This was not true for the other symptoms ($p = 0.18$–0.94). There were no significant correlations between N1 suppression and the four SAPS global scores ($p = 0.24$–0.78) in the ESZ group.

Heterogeneity of suppression-age relationship among groups

The main HC model used for age correction revealed statistically significant evidence of a relationship between N1 suppression and age ($r = 0.3095$, $p = 0.0015$) with N1 suppression increasing 0.25394 μV with each year of age. To test for group difference in the N1 suppression relationship with age, N1 amplitude suppression was regressed on age, group, and age × group interaction terms. The *F*-test for homogeneity of slopes (test of the group × age interaction term) showed a marginally significant group difference in slopes ($F_{2,252} = 2.8753$, $p = 0.05825$). Because there was evidence of a significant age-suppression relationship in the HC, we followed up this marginal effect by testing for slope differences between the HC and CHR ($t_{(252)} = -0.319$, $p = 0.75$) as well as between HC and ESZ ($t_{(252)} = -2.378$, $p = 0.0182$). The latter test indicates that relative to the age-related increase in HC, ESZ showed no such age relationship. Accordingly, when expressed as age-adjusted *z*-scores, ESZ showed increasingly deficient N1 suppression with age ($r = -0.2797$, $p = 0.0099$; online Supplementary Figure, bottom right). Scatterplots of these N1 suppression relationships with age are shown for both raw amplitudes and age-adjusted *z*-scores to demonstrate how the age-adjustment procedure removes the normal aging effect (online Supplementary Figure, top right) but retains pathological aging effects in the clinical groups (online Supplementary Figure, middle and bottom right).

Discussion

The primary aim of this study was to assess speech-related N1 suppression in CHR patients, using a larger sample than was available previously. We now show, for the first time, that suppression of N1 during talking compared with listening is significantly altered in CHR patients. That is, abnormal N1 suppression is not progressive and is evident before many of the sequelae of chronic illness emerge (e.g. chronic disability and medication exposure, long standing social, and occupational dysfunction).

Surprisingly, the ESZ and CHR groups showed equivalent amounts of suppression, in spite of the fact that very few of the CHR sample had converted to a diagnosis of psychosis. Details of N1 suppression are worth considering in light of this. Suppression is calculated by subtracting N1 during Listen from N1 during Talk, and a small suppression value can result from a small N1 during Listen or a large N1 during Talk, or both. ESZ had significantly smaller N1s during Listen, as reported in the literature [reviewed in Rosburg *et al.* (2008)], but did not have larger N1s during Talk. The CHR patients did not have significantly reduced N1s during Listen, but tended to have larger N1s during Talk. So, while their suppression values are not different, the components of the suppression score are.

Feinberg initially proposed that disruptions in the corollary discharge mechanism in schizophrenia blurred the distinction between mental events that occur from endogenous neural activity, from the neural activity generated from external stimuli (Feinberg, 1978). In the current study, attenuated speech-related N1 suppression was related to unusual thought content in the CHR patients but not in the ESZ patients.

With this expanded sample, we were also able to show the effects of age on N1 suppression. With increasing age, N1 suppression increased, approaching an increasingly normal pattern. Interestingly, ESZ patients showed the opposite pattern, with N1 suppression slightly decreasing with age, with older patients showing a greater abnormality. This is difficult to understand in light of other ERP data showing schizophrenia accelerates the normal effects of aging (Pfefferbaum *et al.*, 1984). Caution is warranted in interpreting this weak relationship. It is also worth noting that this relationship was not seen when we included HC up to age 59 years to match chronic schizophrenia patients (Perez *et al.*, 2012). Perhaps the correlation between age and N1 suppression in young HCs is compromised by the accumulation of age-associated illnesses.

This study demonstrates that putative corollary discharge dysfunction during speech occurs in people at high clinical risk for schizophrenia, before the inevitable sequelae of chronic illness, and remains reduced in patients early in the course of their illness, consistent with what we have shown in chronic patients (Ford *et al.*, 2001, 2007*a*, 2007*b*, 2013; Heinks-Maldonado *et al.*, 2007). Importantly, the dysfunction we see in the high-risk individuals is especially prominent in individuals with unusual thought content.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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