Review

Biological Psychiatry: CNNI

Speaking-Induced Suppression of the Auditory Cortex in Humans and Its Relevance to Schizophrenia

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ABSTRACT

Speaking-induced suppression (SIS) is the phenomenon that the sounds one generates by overt speech elicit a smaller neurophysiological response in the auditory cortex than comparable sounds that are externally generated. SIS is a specific example of the more general phenomenon of self-suppression. SIS has been well established in nonhuman animals and is believed to involve the action of corollary discharges. This review summarizes, first, the evidence for SIS in heathy human participants, where it has been most commonly assessed with electroencephalography and/or magnetoencephalography using an experimental paradigm known as "Talk-Listen"; and second, the growing number of Talk-Listen studies that have reported subnormal levels of SIS in patients with schizophrenia. This result is theoretically significant, as it provides a plausible explanation for some of the most distinctive and characteristic symptoms of schizophrenia, namely the first-rank symptoms. In particular, while the failure to suppress the neural consequences of self-generated movements (such as those associated with overt speech) provides a prima facie explanation for delusions of control, the failure to suppress the neural consequences of self-generated inner speech provides a plausible explanation for certain classes of auditory-verbal hallucinations, such as audible thoughts. While the empirical evidence for a relationship between SIS and the first-rank symptoms is currently limited, I predict that future studies with more sensitive experimental designs will confirm its existence. Establishing the existence of a causal, mechanistic relationship would represent a major step forward in our understanding of schizophrenia, which is a necessary precursor to the development of novel treatments.

Keywords: Auditory-evoked potentials, Corollary discharge, Efference copy, First-rank symptoms, Inner speech, N1 suppression, Schizophrenia, Self-suppression

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Self-suppression—also known as sensory attenuation—refers to the phenomenon that self-generated stimuli tend to feel less salient, and evoke a smaller neurophysiological response, than externally generated stimuli that are physically identical (1). While the normative difficulty of tickling oneself is often considered the archetypal example of self-suppression [(2,3); see also Shergill *et al.* (4)], speaking-induced suppression (SIS) of the auditory cortex is another well-established example of the phenomenon (5–7). SIS is the phenomenon that sounds generated by willed vocalizations elicit a smaller neurophysiological response in the auditory cortex than do sounds that are externally generated. As summarized by Eliades and Wang (8), the phenomenon of SIS has been well established in nonhuman animals and is believed to reflect the action of corollary-discharge–related mechanisms. This article attempts to summarize the evidence for SIS in human participants and reviews the growing number of studies indicating that people with schizophrenia exhibit subnormal levels of SIS, which is suggestive of corollary-discharge–related deficits in this patient group. This apparent failure to suppress the sensory consequences of a self-generated action (overt speech) is theoretically significant, as it could provide a direct and plausible explanation for some of the most characteristic and distinctive symptoms of schizophrenia, namely the first-rank symptoms. This review concludes with a discussion of some recent work whose results suggest that SIS not only occurs in response to overt speech, but also is elicited by the production of inner speech—the silent production of words in one's mind. These results are intriguing as they provide a potential link between SIS deficits and the most common psychotic symptom in schizophrenia, namely auditory-verbal hallucinations. In conclusion, by understanding the mechanistic basis of SIS—and self-suppression more generally—this field of research has the capacity to provide significant insights into the mechanistic basis of schizophrenia. Such understanding is of critical importance, as it provides a foundation for the development of novel, evidence-based treatments for the disorder.

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EVIDENCE FOR SIS OF THE AUDITORY CORTEX IN HUMANS

Quantifying SIS in Human Participants

There is substantial evidence from single-unit recording studies that the activity of (some) auditory cortex neurons are suppressed during the production of willed vocalizations in nonhuman primates (8) and other nonhuman animals (9,10). Similar results have also been reported in human participants undergoing neurosurgery: single-unit electrodes placed in the exposed temporal cortex in humans revealed suppressed neuronal firing rates in the auditory cortex when participants produced willed speech, compared with when listening to others speaking (11,12). [It should also be acknowledged that these single-unit recording studies also identified regions where neuronal firing rates were increased in response to speech (9,12), suggesting that speaking has a more nuanced impact on neural activity than simply a globally suppressive effect.]

While single-unit recording studies provide the most direct evidence of SIS, their invasive nature has precluded their widespread use in humans. The vast majority of human research on SIS has used the noninvasive techniques of electroencephalography (EEG) and magnetoencephalography (MEG) to infer the global activity of the auditory cortex. The basic experimental paradigm has been dubbed the Talk-Listen task and is described in detail elsewhere (13). The typical protocol consists of 2 conditions: talk and listen. In the talk condition, participants are instructed to make a series of discrete vocalizations while EEG/MEG data are continuously recorded. Participants are typically instructed to repeatedly vocalize a single syllable (e.g., "ah") every couple of seconds; the precise timing of each vocalization can be either self-determined or prompted by means of a visual cue. In the talk condition, each self-produced sound is routed directly to participants' headphones in real time. In the listen condition, the train of sounds recorded in the talk condition are played back to the participant while he or she sits passively. In other words, the sounds are self-produced in the talk condition but externally produced in the listen condition. Each individual sound elicits an auditory-evoked potential in the EEG/MEG. These waveforms are averaged across trials (for each participant) to generate an average auditory-evoked potential for both the talk and listen conditions.

N1 Suppression

The amplitude of the N1 component of the auditory-evoked potential has been the dependent variable in the majority of published Talk-Listen task studies. The N1 is a large negative deflection in the auditory-evoked potential that occurs approximately 100 ms after the onset of a sound. The N1 is believed to have sources in the primary and secondary auditory cortices (14,15) (see Figure 1Ai, ii). Critically, the N1 is known to be highly sensitive to sound intensity: lower-intensity sounds elicit smaller N1 amplitudes than higher-intensity sounds do (15,16) (see Figure 1Aiii, iv). The MEG equivalent of the N1 is known as the M100.

The most common finding in previous Talk-Listen task studies has been of reduced N1 amplitude in the talk condition relative to the listen condition. This effect, which has been dubbed N1 suppression, has been reported in over 30 published studies (5–7,17–50). N1 suppression has most often been calculated as a difference score (i.e., the difference in N1 amplitude between the talk and listen conditions), though it has sometimes been calculated as a ratio score [e.g., (listen − talk)/listen (5)]. The significance of the N1-suppression effect lies in the fact that the auditory stimuli are, ideally, equally intense in both conditions and thus would be expected to elicit equivalent N1 amplitudes, other factors being equal. [In fact, bone conduction of the sounds generated in the talk condition could potentially lead to their being more intense at the ear than in the listen condition. As has been noted previously (13), this would actually work against the phenomenon of N1 suppression in which N1 amplitude in the listen condition is greater than in the talk condition, which would make the effect even more compelling.] In summary, the phenomenon of N1 suppression has been assumed to reflect the brain processing self-generated vocalizations as though they were physically softer than externally generated sounds. Behavioral studies have provided some evidence in support of this assumption (51).

N1 Suppression Depends on the Degree of Overlap Between Predicted and Actual Auditory Feedback

As illustrated in Figure 1B, the phenomenon of N1 suppression has been assumed to reflect the action of a corollary-discharge–related mechanism, in which a copy of the motor efference driving the speaking-related movements is used to predict the expected sensory properties of the resulting sound, such as its pitch, duration, onset, and so on (9,10,13,52–55). Consistent with leading models of motor control (56–58), this assumption is supported by the fact that the degree of N1 suppression can be reduced by manipulating participants' auditory feedback, such that the expected feedback no longer matches the actual feedback. Several studies have used a variation of the basic Talk-Listen task to compare the N1 amplitude elicited by unaltered vocalizations to those elicited by vocalizations that have been altered in some way, such as by artificially modifying their pitch. These studies have typically reported N1 amplitude to be larger in response to altered (i.e., unpredicted) auditory feedback compared with unaltered (predicted) auditory feedback (17,23,24,59). Furthermore, these studies have often observed an association between the extent to which a participant's vocalizations have been altered and the amplitude of their N1 component, as illustrated in Figure 1C. The above studies demonstrate that SIS is at least partially dependent on the overlap between predicted and actual auditory feedback. However, it is also notable that some degree of SIS occurs even in the case where the auditory feedback is not of the participant's own voice but is instead a nonspecific auditory probe (e.g., a pure tone or burst of white noise) (38,60). Taken together, these results suggest that SIS is partially, but not entirely, dependent on the degree of overlap between predicted and actual auditory feedback. Nonspecific factors (such as the effect of motor-evoked potentials in the talk condition) may also contribute to the effect.

In summary, the results of the noninvasive EEG/MEG studies in humans are broadly consistent with the results of the single-unit studies in nonhuman animals: self-produced vocalizations

elicit smaller N1 amplitudes in the auditory-evoked potential than do externally produced vocalizations. Furthermore, the magnitude of this N1-suppression effect can be reduced by modifying participants' auditory feedback to their own vocalizations. Taken together, these results suggest that the brain makes predictions about the expected auditory consequences of its own vocalizations and suppresses the resultant activity in the auditory cortex to the extent that these predictions match the actual auditory feedback. This idea is consistent with the notion that N1 suppression is underpinned by a corollary-discharge–related mechanism—a notion that has been incorporated into general models of motor control (58,61) and models of speech motor control specifically (55,62,63).

While space constraints preclude a more detailed discussion of the neural networks involved in SIS and motor control more generally [see (9,58,61,61–66) for models and reviews], in the context of speech production, the efference copy has often been depicted as traveling directly from motor and speech production areas in the frontal lobe (e.g., Broca's area) to the auditory cortex in the temporal lobe (40,67,68); for example, see Figure 1Bi. There is evidence that SIS involves communication between the frontal and temporal lobes. For example, the production of willed speech is associated with increased coherence between frontal and temporal electrodes in healthy participants (39,40), and N1 suppression has been shown to correlate with structural integrity of the arcuate fasciculus, which connects the frontal and temporal cortices (47). However, there is growing evidence to suggest that the neural networks underlying SIS are more complicated than a simple frontotemporal connection. There are now numerous studies from both the speech production and motor control literatures suggesting that the cerebellum is critically involved in this network (53,69–72) (see Figure 1Bii). The parietal cortex has also been implicated (72–75). In summary, further research is required to definitively establish the neural networks involved in SIS, including the origin of the efference copy, the destination of the corollary discharge(s), and the specific details of the intervening neural cascade.

SIS OF THE AUDITORY CORTEX IS REDUCED IN PEOPLE WITH SCHIZOPHRENIA

Schizophrenia is a severe mental illness with a lifetime prevalence of slightly less than 1% (76). The neurophysiological basis of the disorder remains poorly understood, and as a consequence, the available treatment options for schizophrenia are highly imperfect (77–79). The key to establishing the neurophysiological basis of schizophrenia lies in understanding the mechanisms that give rise to its distinctive symptoms.

Schizophrenia is a psychotic disorder, which is to say it is characterized by the presence of hallucinations (abnormal perceptions) and delusions (abnormal beliefs) (80,81). Some psychotic symptoms are considered particularly characteristic of schizophrenia: these are known as the first-rank symptoms (82–84). The first-rank symptoms include certain types of auditory-verbal hallucinations (e.g., audible thoughts; voices commenting on one's actions) and certain types of delusions (e.g., delusions of control, delusions of thought insertion/withdrawal/broadcasting). A critical common feature of these first-rank symptoms is that they seem to reflect the misattribution of self-generated actions and thoughts to external forces (85,86); this feature is not as apparent in other (non-first-rank) symptoms commonly experienced in schizophrenia, such as persecutory delusions and formal thought disorder. In a delusion of control, for example, the individual feels as though his or her physical actions—such as the movements associated with the production of overt speech—are being manipulated by an external agent: "Someone makes me move my mouth, my jaw, and pushes the words out. I can't help but say something" (87). Given the role that corollary discharges have been argued to play in enabling animals to distinguish between self-generated and externally generated sensations (9,10,57,88), the fact that (some) first-rank symptoms seem to reflect confusion between self- and externally generated actions and thoughts has led to the theory that these symptoms ultimately arise from corollary-discharge–related abnormalities (85,86).

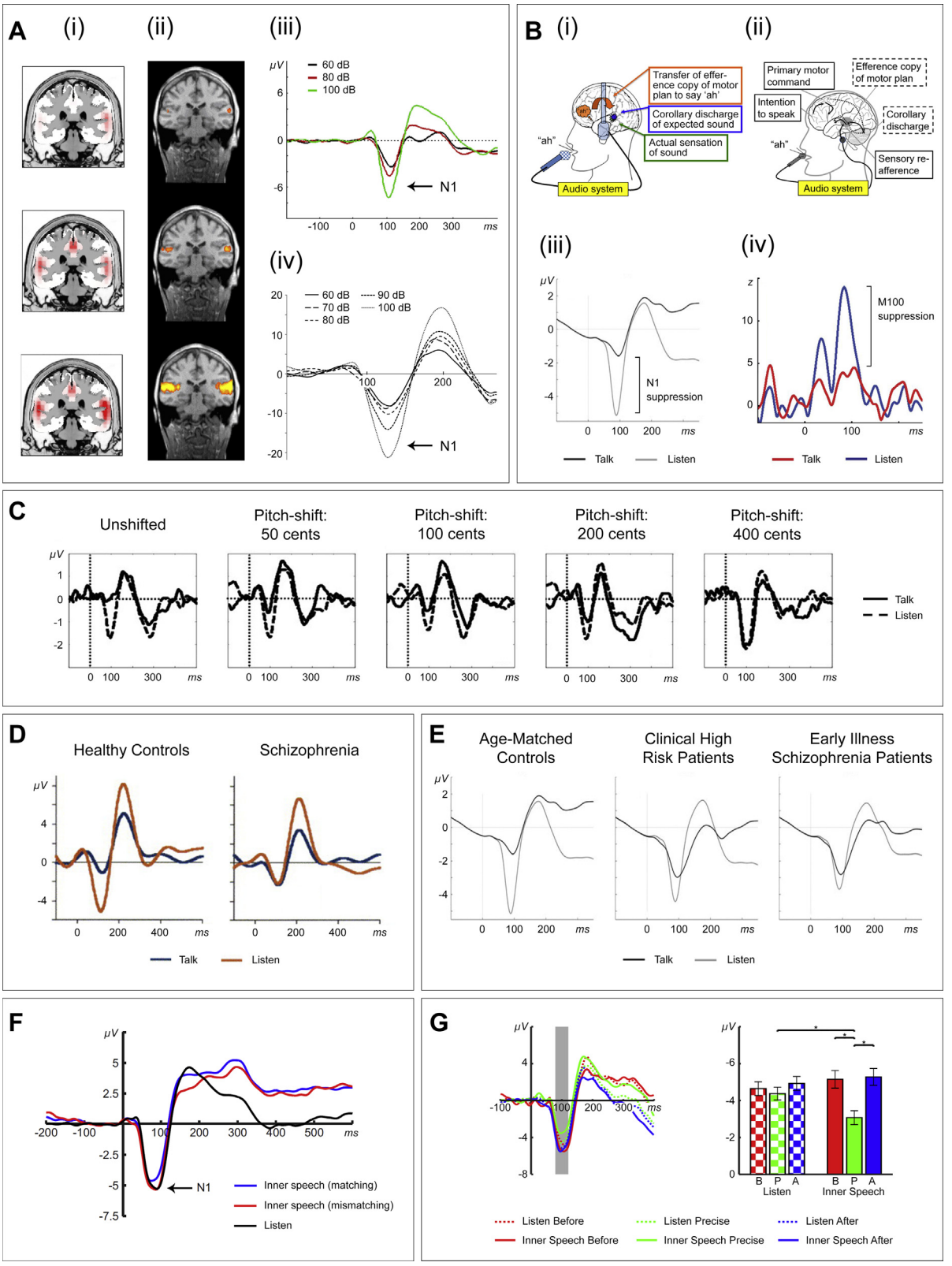
N1-Suppression Deficits in Schizophrenia

Empirical support for the corollary-discharge theory of schizophrenia (85,86) has been provided by 14 Talk-Listen task studies that have investigated for N1-suppression deficits to speech in patients with schizophrenia—these studies are summarized in Table 1. In general, these studies have found that patients with schizophrenia exhibit lower levels of N1 suppression to their own willed speech than do matched healthy control subjects; see Figure 1D for a representative result. Regarding the basis of these N1-suppression deficits, most studies observed patients with schizophrenia to show smaller N1 amplitudes in the listen condition, but greater N1 amplitudes in the talk condition, relative to healthy control subjects. In addition to N1-suppression deficits, other studies have also reported reduced coherence between frontal and temporal electrodes during talking in patients with schizophrenia, at delta and theta frequency bands (39). (In this context, coherence refers to the cross correlation of normalized power spectra between electrode pairs.) Finally, Ford *et al.* (41) also reported reductions in intertrial coherence (i.e., correlations in phase within a single electrode, across trials) in patients with schizophrenia in the period around speech onset in the talk condition.

As an aside, there is growing evidence to suggest that the N1-suppression deficits exhibited by patients with schizophrenia are not limited to speaking, but are also present when patients produce sounds by other means, such as by pressing a button to produce a tone (89,90). There is also evidence that people with schizophrenia show abnormalities in sensory prediction tasks that do not involve the auditory system at all, such as those involving saccades and smooth-pursuit eye movements (91–93); see (72) for a recent review of the evidence for multisensory prediction deficits in schizophrenia. Taken together, these results raise the question of whether the self-suppression deficits observed in schizophrenia are due to SIS abnormalities per se or whether they are indicative of a more general deficit in sensory prediction (94–98).

N1-Suppression Deficits in Other Psychotic and High-Risk Populations

While SIS deficits have been most commonly reported in people with schizophrenia, there is some evidence that they also occur in people with other psychotic disorders and in high-risk populations. For example, Ford *et al.* (44) found that while patients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Listen
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Pitch-shift: 50 cents
Pitch-shift: 100 cents
Pitch-shift: 200 cents
Pitch-shift: 400 cents
Talk
Listen
D
Healthy Controls
Schizophrenia
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Clinical High Risk Patients
Early Illness Schizophrenia Patients
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Inner speech (matching)
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Listen
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Listen Before
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Listen After
Inner Speech Before
Inner Speech Precise
Inner Speech After
B P A
Listen
Inner Speech

with schizophrenia showed the greatest reductions in N1 suppression in the Talk-Listen task relative to healthy control subjects, patients with bipolar I disorder with a history of psychotic symptoms also exhibited subnormal levels of N1 suppression, and schizoaffective patients showed a (nonsignificant) trend in this direction. In contrast, the unaffected relatives of the patients with schizophrenia, schizoaffective disorder, and bipolar disorder did not show any evidence of N1-suppression deficits relative to control subjects.

There is also evidence for N1-suppression deficits in individuals at clinical high risk (CHR) of developing a psychotic disorder. In general, these studies have found that CHR participants exhibit N1-suppression levels that are intermediate between patients with schizophrenia and healthy control subjects (43,47,48) (see Figure 1E). In their recently published final report on a long-term research project, Mathalon *et al.* (48) reported that CHR individuals showed N1-supppression levels that were intermediate between patients with chronic schizophrenia and healthy control subjects: specifically, the CHR participants exhibited (significantly) less N1 suppression than the control subjects did but (nonsignificantly) more N1 suppression than the patients with schizophrenia did. Finally, Oestreich *et al.* (28) reported evidence of N1-suppression deficits in nonclinical individuals who scored highly on a psychometric measure of schizotypy. Oestreich *et al.* (28) recruited first-year university students without a psychiatric diagnosis and divided them into high versus low schizotype groups based on their score on the Schizotypal Personality Questionnaire (99). They found that students categorized as high schizotype exhibited significantly less N1 suppression in the Talk-Listen task than did those categorized as low schizotype. The similarities between these results and those of the aforementioned CHR studies is perhaps unsurprising given the close conceptual association between high schizotypy and the CHR category of attenuated psychotic symptoms (100,101).

THE (HYPOTHESIZED) RELATIONSHIP BETWEEN SIS AND THE FIRST-RANK SYMPTOMS OF SCHIZOPHRENIA

Arguably the greatest strength of the corollary-discharge theory of schizophrenia (85,86) lies in its ability to provide a direct

Figure 1. **(A)** The auditory N1 component has generators in the primary auditory cortex. **(i)** Current source density activations identified with electroencephalography–low-resolution electromagnetic tomography to 60-dB sound pressure level tones (top row), 80-dB sound pressure level tones (middle row), and 100-dB sound pressure level tones (bottom row). **(ii)** Functional magnetic resonance imaging–blood oxygen level–dependent activity in the primary auditory cortex to the same stimuli. **(iii)** The auditory N1 is intensity dependent. The amplitude of the auditory N1 component increases with sound intensity in a positive monotonic fashion. Images (i), (ii), and (iii) reproduced and modified from Mulert *et al.* (16) with permission of Elsevier. **(iv)** A second depiction of the positive monotonic relationship between sound intensity and N1 amplitude. Image reproduced and modified from Hagenmuller *et al.* (125) with permission of Elsevier. **(B)** Quantifying speaking-induced suppression (SIS) in humans with the Talk-Listen task paradigm. In the talk condition of the Talk-Listen task paradigm, participants typically repeatedly vocalize a single word or syllable, such as the syllable "ah." The sound generated by each vocalization is routed to the participant's headphones in real time. In the listen condition, participants passively listen to the sequence of vocalizations recorded in the talk condition. **(i)** A schematic of a (simple) neural network such as could potentially underlie SIS. An efference copy initiated in (frontal) speech production areas projects to the auditory cortex, where it generates a neural prediction regarding the expected auditory properties of the speech (a corollary discharge). This sensory prediction is compared with auditory-evoked activity in the auditory cortex. Image reproduced and modified from Wang *et al.* (20) with permission of Elsevier. **(ii)** A schematic of a (more complex) neural network such as could potentially underlie SIS. An efference copy generated in frontal lobe projects to the cerebellum where it generates a corollary discharge. This sensory prediction is sent to the auditory cortex where it is compared with the auditory-evoked activity. Image created by Judith Ford. **(iii)** The phenomenon of N1 suppression. N1 suppression refers to the finding that N1 amplitude is normatively reduced in the talk condition relative to the listen condition, despite the fact that the auditory stimuli are (ideally) equally intense in the both conditions. This figure shows an example of N1 suppression identified with the Talk-Listen task in healthy participants. Image reproduced and modified from Mathalon *et al.* (48) with permission of Cambridge University Press. **(iv)** M100 suppression. The M100 component is the magnetoencephalography equivalent of the N1. This figure shows an example of M100 suppression identified with the Talk-Listen task in healthy participants. Note that the magnitude of the M100-suppression effect in this example is larger than that typically observed in SIS studies. This is because the waveforms were averaged from trials in which the acoustics of the self-produced syllable fell close to the center of each participant's formant distribution. Image reproduced and modified from Niziolek *et al.* (22) with permission of the Society for Neuroscience conveyed through the Copyright Clearance Center, Inc. **(C)** The magnitude of the N1-suppression effect depends on the degree of overlap between predicted and actual auditory feedback. N1 suppression is maximal when the participant's voice is unaltered (i.e., un-pitch-shifted) in the talk condition (leftmost waveform). Pitch shifting the participant's voice by 400 cents (1 semitone = 100 cents) completely eliminates the N1-suppression effect (rightmost waveform). Intermediate levels of pitch shifting result in intermediate levels of N1 suppression (middle waveforms). Image reproduced and modified from Behroozmand and Larson (23) under the terms of the Creative Commons Attribution License. **(D)** Patients with schizophrenia show subnormal levels of N1 suppression. Patients with schizophrenia, compared to healthy control subjects, have consistently been found to show less N1 suppression in the Talk-Listen task. This N1-suppression deficit has often been found to due to patients with schizophrenia exhibiting smaller N1 amplitudes in the listen condition, but larger N1 amplitudes in the talk condition, relative to matched healthy control subjects. Image reproduced and modified from Ford and Mathalon (117) with permission of Elsevier. **(E)** Individuals at clinical high risk of developing a psychotic disorder show levels of N1 suppression that are intermediate between healthy control subjects and patients with schizophrenia. Image reproduced and modified from Mathalon *et al.* (48) with permission of Cambridge University Press. **(F)** N1 suppression to inner speech. The production of a phoneme in inner speech (e.g., "ba") results in N1 suppression to a simultaneously presented audible probe, but only if the content of the inner phoneme matches the content of the audible probe (e.g., inner phoneme "ba," audible phoneme "ba")—see the inner speech (matching) condition (blue line). If the content of the inner phoneme does not match the content of the audible phoneme (e.g., inner phoneme "ba," audible phoneme "bi"), no N1 suppression occurs—see the inner speech (mismatching) condition (red line). As per standard practice, N1 suppression is calculated relative to a passive listening condition—see the listen condition (black line). Image modified from Whitford *et al.* (120) under the terms of the Creative Commons Attribution License. **(G)** N1 suppression to inner speech is precisely time-locked to its onset. The production of inner speech is associated with reduced N1 amplitude to a matching auditory probe, but only when the inner speech and auditory probe occur concurrently (Inner Speech Precise condition; solid green bar). If the auditory probe is presented 300 ms before the auditory probe (Inner Speech Before condition; solid red bar) or 300 ms after the auditory probe (Inner Speech After condition; solid blue bar), no reduction in N1 amplitude is observed. Varying the onset of the auditory probe has no effect on N1 amplitude in the Listen conditions, in which no inner speech is produced (checked bars). Significant between-condition differences are indicated with asterisks. Image reproduced and modified from Jack *et al.* (121), with permission of Elsevier.

Table 1. A Summary of the 14 Studies That Used the Talk-Listen Task to Investigate for Deficits in SIS in Patients With Schizophrenia and Other Clinical Populations

Study	Sample	What Sounds Did Participants Produce in Talk?	What Sounds Did Participants Hear in Listen?	Dependent Variables	Key Results	Clinical Correlations	Other Results/ Comments
Ford *et al.* (37), 2001	7 SZ; 7 HC	Syllables; [ah] on 80% of trials, [ay] on 20% of trials	Syllables recorded in talk	N1 suppression	Sig. group (HC, SZ) × condition (talk, listen) interaction Sig. N1 suppression in HC; not in SZ	Not investigated	
Ford *et al.* (38), 2001	12 SZ; 10 HC	Full sentences; typical hallucinatory statements (e.g., "that was really stupid")	Auditory probes: 1. Syllables ([ba]) 2. Noise-bursts (broadband) Visual probes: 1. Checkerboard stimuli	N1 suppression	Sig. group (HC, SZ) × condition (talk, listen) interaction Sig. N1 suppression to auditory probes in HC; not in SZ No sig. group × condition interaction for visual probes	No No correlations between N1 suppression/amplitude/latency and BPRS (Hallucinatory Behavior, Unusual Thought Content) and SAPS (Global Hallucinations, Global Delusions) scores	N1 latency: later for HC P2 amplitude: no sig. group × condition interaction
Ford *et al.* (39), 2002	12 SZ; 10 HC	As per Ford *et al*. (38)	As per Ford *et al.* (38)	EEG coherence (frontotemporal) for delta, theta, alpha, beta, gamma frequency bands. (Coherence here refers to the spectral cross correlation between pairs of electrodes)	Increased coherence (frontotemporal) to talk in all frequency bands in HC Sig. group (HC, SZ) × condition (talk, listen) in delta and theta frequency bands, driven by patients with SZ failing to show increased coherence to talk	Yes Patients subdivided into hallucinators (BPRS Hallucinatory Behavior ≥5) vs. nonhallucinators (BPRS Hallucinatory Behavior ≤2) Hallucinators showed no coherence increase to talk, nonhallucinators showed coherence levels between hallucinators and HC	Fully overlapping sample with Ford *et al.* (38)
Ford *et al.* (40), 2005	20 SZ; 21 HC	Syllables [ah]	Syllables recorded in talk; auditory feedback was undistorted, pitch shifted (half semitone), or pitch shifted (1 semitone)	EEG coherence (frontotemporal/parietal) in gamma frequency band (5 subbands)	Increased gamma-band coherence to talk vs. listen in HC; smaller effect in SZ Pitch shifting resulted in reduced gamma band coherence to talk in HC, but not SZ	No No correlations between gamma band coherence difference scores (Talk-Listen) on BPRS (Hallucinatory Behavior, Unusual Thought Content, Conceptual Disorganization, Total) or SAPS (Voices Commenting, Voices Conversing, Hallucinations Summary) scales Patients subdivided into hallucinators vs. nonhallucinators (based on average BPRS and SAPS scores): no between-group differences in gamma band coherence	

Table 1. Continued

Study	Sample	What Sounds Did Participants Produce in Talk?	What Sounds Did Participants Hear in Listen?	Dependent Variables	Key Results	Clinical Correlations	Other Results/ Comments
Ford *et al.* (126), 2007	27 SZ/SZAF; 26 HC	Syllables [ah]	Syllables recorded in talk Also included an "expectancy" condition in which the temporal onset of the syllables were visually cued in listen	N1 suppression	Sig. group × condition interaction: significant N1 suppression to talk in HC but not SZ The interaction was not due to group differences in the expectancy condition N1 amplitude higher to listen but lower to talk in HC vs. SZ	No No correlations between N1 suppression and any BPRS item in SZ	Also implemented a Press-for-Tone task, which elicited less N1 suppression than the Talk-Listen task did in HC
Ford *et al.* (41), 2007	24 SZ/SZAF; 25 HC	Syllables [ah]	Syllables recorded in talk	N1 suppression; Intertrial coherence at electrode FCz in 15–47 Hz frequency band	N1 suppression: sig. group × condition interaction, due to sig. N1 suppression in HC but not SZ Intertrial coherence was greater in the prestimulus period in talk vs. listen in both HC and SZ. However the effect was significantly stronger in HC Sig. correlation between pretalking intertrial coherence and N1 suppression in HC, but not SZ	Yes Pretalking intertrial coherence negatively correlated with BPRS hallucinations (controlling for BPRS avolition/apathy)	
Heinks-Maldonado *et al.* (42), 2007	20 SZ; 17 HC	Syllables [ah]	Syllables recorded in talk (self-condition) or syllables produced by another person (alien condition) The syllables were either undistorted, or pitch shifted (2 semitones)	N1 suppression	Patients were subdivided into hallucinators vs. nonhallucinators. Hallucinators scored ≥2 on a composite hallucinations score, which was the sum of the SAPS Auditory Hallucinations, Voices Commenting, Voices Conversing subscales N1 suppression: HC > nonhallucinators > hallucinators	Yes In addition to the aforementioned between and within group differences, there was a sig. negative correlation between N1 suppression and global SAPS-Hallucinations Scale No sig. correlation with global SAPS-Delusions Scale	

Table 1. Continued

Study	Sample	What Sounds Did Participants Produce in Talk?	What Sounds Did Participants Hear in Listen?	Dependent Variables	Key Results	Clinical Correlations	Other Results/ Comments
Perez *et al.* (43), 2012	75 SZ; 77 HC; 35 CHR	Syllables [ah]	Syllables recorded in talk	N1 suppression	N1 suppression: HC > CHR > SZ N1 amplitude to listen reduced in SZ vs. HC N1 amplitude to talk increased in SZ vs. HC CHR showed intermediate levels of N1 suppression between HC and SZ	No No sig. correlation between N1 suppression and PANSS-Positive-Total or PANSS-Negative-Total scores in SZ No sig. correlation between N1 suppression and SOPS-Positive or SOPS-Negative summary scores in CHR	
Ford *et al.* (44), 2013	30 SZ; 19 SZAF; 39 BPP; 30 RSZ; 23 RSZAF; 50 RBPP; 43 HC	Syllables [ah]	Syllables recorded in talk	N1 suppression	Sig. group × condition (talk, listen) interaction N1 suppression: HC = RSZ = RSZAF = RBPP > SZ = SZAF = BPP	No No sig. correlations between N1 suppression and PANSS-Positive-Total, PANSS-Hallucinations, YMRS, or MADRS scores	
Buhler *et al.* (45), 2016	28 SZ; 28 HC	Single words	(a) Word from talk in own voice (b) Word from talk in alien voice (c) Listen in own voice (d) Listen in alien voice	N1 amplitude	Agency: (a) − (b) vs. (c) − (d) Sig. group × condition interaction on N1 amplitude SZ showed less N1 suppression than HC; no sig. differences between hallucinators and nonhallucinators Ownership: (a) − (c) vs. (b) − (d) No sig. group × condition interaction on N1 amplitude	No SZ subdivided into hallucinators (n = 14) vs. nonhallucinations (n = 14) based on medical history; No sig. between group differences in agency or ownership effects; No sig. correlations between agency or ownership effects and PANSS Global or PSYRATS scores	Also investigated a "late component" (172–356 ms): no sig. group × condition interaction
Kort *et al.* (46), 2017	34 SZ; 33 HC	Syllables [ah]	Syllables recorded in talk	N1 suppression	Sig. group × condition interaction Reduced N1 suppression in SZ vs. HC N1 talk was significantly larger for SZ vs. HC No significant between group differences in N1 listen	No No sig. correlations between N1 suppression and PANSS-Positive, PANSS-Negative, or PANSS-General scores in SZ	Also administered ketamine to HC. Ketamine caused a reduction in N1 suppression of comparable magnitude to the N1-suppression deficits exhibited by the SZ

Table 1. Continued

Study	Sample	What Sounds Did Participants Produce in Talk?	What Sounds Did Participants Hear in Listen?	Dependent Variables	Key Results	Clinical Correlations	Other Results/ Comments
Whitford *et al.* (47), 2018	51 ESZ; 40 CHR; 59 HC	Syllables [ah]	Syllables recorded in talk	N1 suppression Structural integrity of the arcuate fasciculus and pyramidal tracts (fractional anisotropy and radial diffusivity)	N1 suppression: HC > CHR > SZ Arcuate integrity: HC = CHR > SZ Sig. correlation between N1 suppression and radial diffusivity in the arcuate Pyramidal integrity: no sig. between group differences	Not investigated	Partially overlapping sample with Perez *et al.* (43)
Mathalon *et al.* (48), 2018	84 ESZ; 71 CHR; 103 HC	Syllables [ah]	Syllables recorded in talk	N1 suppression	N1 suppression: HC > CHR = ESZ ESZ showed reduced N1 amplitude in listen and increased N1 amplitude in talk vs. HC CHR showed intermediate N1 amplitudes to both talk and listen	Mixed No sig. correlations between N1 suppression and global SAPS scores (Hallucinations, Delusions, Thought Disorder, Bizarre Behavior) in ESZ Sig. correlations between N1 suppression and SOPS unusual thought content in CHR	Partially overlapping sample with Perez *et al.* (43) and Whitford *et al.* (47). This sample is reported as being the final sample
Roach *et al.* (49), 2018	49 ESZ/ESZAF; 29 HC	Syllables [ah]	Syllables recorded in talk Explored whether N1-suppression deficits could be ameliorated with TAT (n = 23) vs. CG (n = 26)	N1 suppression	N1 suppression: HC > SZ, pretreatment N1 suppression was improved by TAT, but not CG, in ESZ	No After removing outliers, no sig. correlation between treatment-related change in N1 suppression and change in global SAPS global scores (Hallucinations, Delusions, Thought Disorder, Bizarre Behavior)	

BPP, bipolar disorder with psychosis; BPRS, Brief Psychiatric Rating Scale; CG, computer games; CHR, patients at clinical high risk; EEG, electroencephalography; ESZ, patients with early schizophrenia (typically within 2 years of first episode); ESZAF, patients with early schizoaffective disorder; HC, healthy control subjects; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scales; RBPP, relatives of patients with bipolar disorder with psychosis; RSZ, relatives of patients with schizophrenia; RSZAF, relatives of patients with schizoaffective disorder; SAPS, Scale for the Assessment of Positive Symptoms; sig., significant; SIS, speaking-induced suppression; SOPS, Scale of Prodromal Symptoms; SZ, patients with schizophrenia; SZAF, patients with schizoaffective disorder; TAT, Targeted Auditory Training; YMRS, Young Mania Rating Scale.

and plausible account of the first-rank symptoms. This is particularly true of delusions of control, which have long been conceptualized as reflecting the misattribution of self-generated movements to external sources (102). In light of this, it is somewhat surprising that so few studies have explored the association between N1-suppression deficits and the first-rank symptoms of schizophrenia specifically. The identification of this relationship would represent strong evidence in support of the theory. I believe that this association will be found to exist, but that identifying it will require some modifications to the experimental methodologies employed by previous studies. Some suggested modifications are outlined below; for further discussion of some of these issues, see (103,104).

Insensitive Clinical Ratings

As outlined in Table 1, most previous Talk-Listen task studies have been incapable of investigating the association between N1-suppression deficits and the first-rank symptoms, as they have either used rating scales that do not specifically assess these symptoms, such as the Positive and Negative Syndrome Scale (105) and Brief Psychiatric Rating Scale (106), or used "global" symptom ratings that combine patients' scores on the first-rank symptoms with other non-first-rank psychotic symptoms. Future studies should consider using rating scales such as the Scale for the Assessment of Positive Symptoms (107), which assess each of the first-rank symptoms individually, and should aim to investigate the neurophysiological correlates of specific symptoms rather than using more global, composite measures of symptom severity.

Nonsymptomatic Participants

While the first-rank symptoms are relatively common in schizophrenia at first contact, occurring in around one half of cases [(82), see also (108)], the vast majority of previous Talk-Listen task studies have investigated patients who were taking antipsychotic medication at the time of testing. Given that antipsychotic medications are relatively effective against psychotic symptoms (78), this implies that most previous studies investigated patient samples with artificially low levels of first-rank symptoms. This could potentially obscure the nature of the relationship with N1 suppression. Furthermore, it is also possible that the relationship between N1-suppression deficits and residual symptoms (i.e., symptoms that persist post-treatment) is not the same as that for first-contact symptoms. To avoid these complications, future studies should aim to recruit participants that are antipsychotic naïve. If this is not possible, which is understandable given the significant logistic and ethical challenges involved in this type of research, future studies should aim to recruit a sufficient number of participants with residual first-rank symptoms to ensure adequate statistical power and carefully estimate the effect of medication exposure on N1 suppression in the statistical analysis.

Nonlinear Relationship With Symptoms

As outlined in Table 1, most previous studies have explored the relationship between SIS and clinical symptoms by simply correlating patients' level of N1 suppression against their score on one or more (global) clinical rating scales. It is possible that the relationship between N1-suppression deficits and symptom severity is nonlinear; for example, it may be that while N1-suppression deficits are associated with the presence of first-rank symptoms, N1 suppression does not determine the severity of these symptoms, which instead depends on other factors such as the level of functional impairment they induce. A preferable approach might be to separate patients into subgroups based on their history of a specific symptom (e.g., current delusions of control vs. past history of delusions of control vs. no history of delusions of control) and compare these subgroups on level of N1 suppression. Such a symptom-focused approach (109,110) has been employed by previous neuropathological studies in psychotic populations (111,112). While several of the Talk-Listen task studies outlined in Table 1 used this approach to categorize patients on the basis of the presence or absence of hallucinations in general (39,42,45), no previous studies have attempted this approach in the context of first-rank symptoms specifically. This would be a worthwhile goal for future studies.

SUPPRESSION OF THE AUDITORY CORTEX IN RESPONSE TO INNER SPEECH: AN EXPLANATION FOR AUDITORY-VERBAL HALLUCINATIONS?

In a similar way to how delusions of control have been argued to reflect the misperception of self-generated movements as externally generated movements, some types of auditory-verbal hallucinations have been argued to reflect the misperception of inner speech as being external speech (85,86,113–115). One particularly direct example is the phenomenon of audible thoughts, also known as thought echo. Audible thoughts are a type of auditory-verbal hallucination in which the patient hears his or her own thoughts being spoken out loud, typically by a voice that is not his or her own ["A 32 year old housewife complained of a man's voice, speaking in an intense whisper from a point about 2 feet above her head. The voice would repeat almost all the patient's goal-directed thinking—even the most banal thoughts. The patient would think 'I must put the kettle on,' and after a pause of not more than one second the voice would say 'I must put the kettle on'" (116)]. Audible thoughts are highly characteristic of schizophrenia and are a first-rank symptom.

The phenomenological similarities between delusions of control and audible thoughts raises a question: if delusions of control arise from a failure to suppress the sensory consequences of self-generated movements—such as the SIS associated with overt speech—do audible thoughts arise, in an analogous manner, from the failure to suppress sensory consequences of self-generated inner speech? Does inner speech—the silent production of words in one's mind—even result in suppression of the auditory cortex? Ford *et al.* (37,117,118) attempted to investigate this question using a variant of the Talk-Listen task. In these studies, patients with schizophrenia and matched healthy control subjects listened to a sequence of auditory probes (e.g., a recording of a voice producing the syllable /ba/) while EEG was recorded. The silent baseline condition was analogous to the listen condition in the Talk-Listen task: participants sat passively and listened to the auditory probes. In the inner speech condition, participants were instructed to produce a series of statements in inner

speech while listening to the auditory probes. The statements were designed to be typical of the kinds of statements commonly reported in auditory-verbal hallucinations (e.g., "that was really stupid"). With regard to the results, in the healthy control participants, the auditory probes elicited smaller N1 amplitudes in the inner speech condition relative to the silent baseline condition; that is, the production of inner speech resulted in N1 suppression, even in the absence of any overt movement. This result is significant as it suggests that inner speech per se is associated with suppression of the auditory cortex. In contrast, the participants with schizophrenia did not exhibit N1 suppression in the inner speech condition. This result is consistent with deficits in SIS in patients with schizophrenia and is further suggestive of corollary-discharge–related abnormalities in this population.

The studies of Ford *et al.* (37,117,118) were seminal in providing a methodological framework for quantifying suppression of the auditory cortex in response to inner speech. However, despite their importance, they suffered from some limitations. First, these studies did not attempt to time-lock the inner speech to the auditory probes. Second, they were unable to determine whether the observed N1 suppression was caused by inner speech per se or whether it was influenced by other factors, such as between-condition differences in attention such as could potentially arise from participants being required to produce a mental action in the inner speech condition but not the silent baseline condition. Third, they did not investigate whether N1 suppression was influenced by the degree of overlap between the predicted and actual auditory feedback, which is a key assumption of a corollary-discharge–based account of the effect. Thus, while these studies provided the first evidence that patients with schizophrenia show deficits in auditory-cortex suppression to inner speech, locking down these (theoretically critical) results will require the use of more tightly controlled experimental protocols.

To this end, the experimental designs developed by Tian *et al.* (63,119) and modified by Whitford *et al.* (120) and Jack *et al.* (121) have great potential. In these designs, participants are typically asked to produce a single syllable in inner speech (e.g., "ba"). An auditory probe is then presented, which is ideally tightly time-locked to the inner syllable. The auditory probe can either match the content of the inner speech (e.g., inner speech "ba," auditory probe "ba") or mismatch the content of the inner speech (e.g., inner speech "ba," auditory probe "bi"). Finally, in a control condition analogous to the listen condition in the Talk-Listen task, participants are required to sit passively and listen to the auditory probes. In their 2017 study in healthy participants, Whitford *et al.* (120) found that the production of inner speech resulted in N1 suppression (i.e., relative to the listen condition) but only when the content of the inner speech matched the content of the auditory probe (see Figure 1F). Furthermore, as illustrated in Figure 1G, we recently demonstrated that N1 suppression to inner speech depends on a precise temporal congruence between the inner phoneme and auditory probe: if the auditory probe was presented a fraction of a second before or after the inner phoneme, no N1 suppression was observed (121); see also (122). Taken together, these results indicate that N1 suppression to inner speech is dependent on the extent to which the inner speech and auditory probe match on content and temporal properties, both of which are consistent with a corollary-discharge account of the effect.

In addition to its dependence on the content and temporal properties of inner speech, recent work by Tian *et al.* has demonstrated that inner speech–induced suppression is also influenced by the physical properties of the inner speech. Specifically, Tian *et al.* (123) demonstrated that the level of N1 suppression was dependent on the imagined loudness of inner speech; that is, the N1 amplitude elicited by an auditory probe was smaller when participants imagined themselves speaking loudly compared with when they imagined themselves speaking softly. This fascinating result suggests that inner speech does not exist as abstract, free-floating content, but instead has physical properties, which include loudness but may also potentially include other properties such as pitch, timbre, and regional accent (124). This important result opens up a myriad of possibilities for future research aimed at understanding the symptoms of schizophrenia. For example, is it possible that some auditory-verbal hallucinations are caused by abnormally loud inner speech?

In conclusion, I hypothesize that future studies will identify neurophysiological evidence of inner speech abnormalities in patients with schizophrenia with audible thoughts and potentially also other classes of auditory-verbal hallucinations such as third-person hallucinations. However, to identify this relationship, I believe that future studies will need to employ experimental designs that are sufficiently sensitive to detect this (potentially subtle) effect and carefully consider their approach to such (potentially problematic) issues as ensuring the time-locking of inner speech, reducing between-condition differences in attention, and eliminating the need for overt movements whose evoked activity could confound the psychophysiological changes associated with inner speech per se.

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