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Sensory Attenuation Deficit and Auditory Hallucinations in Schizophrenia: A Causal Mechanism or a Risk Factor? Evidence From Meta-Analyses on the N1 Event-Related Potential Component

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ABSTRACT

BACKGROUND: Sensory attenuation (SA), the dampened perception of self-generated sensory information, is typically associated with reduced event-related potential signals, such as for the N1 component of auditory event-related potentials. SA, together with efficient monitoring of intentions and actions, should facilitate the distinction between self-generated and externally generated sensory events, thereby optimizing interaction with the world. According to many, SA is deficient in schizophrenia. The question arises whether altered SA reflects a sufficient mechanism to explain positive symptoms such as auditory hallucinations. A systematic association of reduced auditory SA in hallucinating patients would support this hypothesis.

METHODS: We conducted a series of meta-analyses on 15 studies on auditory SA in which the N1 component of event-related potential–electroencephalogram signals was measured during talking (self-generated sensory signals condition) or when listening to prerecorded vocalizations (externally generated sensory signals condition).

RESULTS: We found that individuals with schizophrenia did show some auditory SA because their N1 signal was significantly attenuated in talking conditions compared with listening conditions. However, the magnitude of such attenuation was reduced in individuals with schizophrenia compared to healthy control participants. This phenomenon generalizes independently from the stage of the disease, the severity of positive symptoms, and whether patients have auditory hallucinations or not.

CONCLUSIONS: These findings suggest that reduced SA cannot be a sufficient mechanism for explaining positive symptoms such as auditory hallucinations in schizophrenia. Because reduced SA was also present in participants at risk of schizophrenia, reduced SA may represent a risk factor for the disorder. We discuss the implications of these results for clinical-cognitive models of schizophrenia.

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The sensory consequences of voluntary actions are perceived as less intense than those generated by passive or external movements (1,2). This sensory attenuation (SA) represents an important component of efficient self-monitoring processes (3), and it is considered a prerequisite for a veridical experience of self-agency [see (4) for a review]. It follows that precise suppression of sensory consequences of our actions should be essential to efficiently interact with the external environment.

SA has been found to be altered in many different disorders, such as obsessive-compulsive disorder (5), borderline personality disorder (6), chronic pain (7), Parkinson's disease (8,9), and eating disorders (10,11). The exploitation of SA indices in clinical populations has mostly been driven by the fact that SA has long been considered an indirect measure of self-agency.

Schizophrenia and related schizophrenia spectrum disorders are considered a crucial testbed for the very concept of SA (12–14) because SA abnormalities may provide explanations about the mechanisms underlying certain manifestations of the illness; symptoms such as hallucinations and delusions of control could be interpreted as being due to a defective sense of self-agency associated with altered SA processes (15–17). To date, however, there has been no formal assessment of whether SA is absent or only reduced in schizophrenia or of whether the phenomenon depends on the severity/stage of the disorder or the presence of specific symptoms.

Different interpretations have been proposed to explain the phenomenon of SA. Although there is agreement about the crucial role of predictive processes that allow one to distinguish between self- and externally generated sensory consequences, they explain differently how predictions are implemented in the human neurocognitive system [see (18–20) for a review].

The attention hypothesis suggests that attention may be directed toward predictive aspects of the action generation

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rather than the produced sensory stimuli. Consequently, self-generated stimuli are perceived as less intense than externally generated stimuli to which attention is completely focused during perception [see, for example (21–24)].

On the other hand, cancellation models (3,25) postulate that motor predictions are used to suppress the expected sensory outcome. When a voluntary movement is produced, an efference copy of the motor command is used through an internal forward model to produce corollary discharges (26–28), carrying predictions about the sensory consequences of the movement. These predictions are then compared with the actual sensory effects of the actions, and in the case of matching, they are used to attenuate the perception of sensory feedback itself (2,3,29,30).

Finally, the pre-activation theory suggests that motor program representations are accompanied by their most plausible sensory consequences, pre-activating and preparing for a specific percept (i.e., increased activity in the sensory areas that represent expected action outcome). Consequently, if the actual sensory consequences match the predicted representation, the self-generated sensation will have a less perceptual impact in terms of brain activations (31,32).

Cancellation models and pre-activation theories have been further elaborated in the framework of the predictive coding theories and Bayesian accounts (19,33–38), according to which our brain constantly tries to infer the cause of incoming sensory information by balancing between prior beliefs about the cause of changes in perceptions and the actual sensory evidence [e.g., by varying the weights on sensory channels and assigning higher importance to expected rather than unexpected sensory events, as in sharpening models (19,37,38)]. More specific details on these different theoretical models are reported in Table 1.

Auditory SA and Theories of Hallucinations in Schizophrenia

SA occurs across various sensory modalities, including vision, touch, and audition. In the auditory domain, SA is usually measured through noninvasive recording of event-related potentials of the electroencephalography signal targeting response from the N100-P200 (N1-P2) complex, which normally originates from the auditory cortex following auditory stimulation. Auditory stimuli elicit a series of event-related potentials, which mainly consist of 2 peaks: N1 is the first negative peak, recurring after almost 100 ms from auditory stimulus presentation; and P2 is the second positive peak, with a latency of 200 ms. N1 has been widely investigated, and its subcomponents and topographical distribution have been identified [nonspecific N1, vertex-negative wave; supratemporal N1, a fronto-centrally predominant component; and T-complex, which is generated in the lateral portion of the superior temporal lobe, thus in the secondary auditory cortices (39)]. The N1 component is reduced when talking compared with passive listening to spoken sounds [see, e.g., (40–42)].

Unfortunately, evidence about the P2 component is not as extensive. The few available data are not consistent in showing suppression of this positive component in the context of self-generated actions. Moreover, most of the studies that have investigated auditory SA in people with schizophrenia measured only the N1 component. For these reasons, here we concentrate on the reduction of the N1 response only, which will be the dependent variable in all the meta-analyses described below.

Previous studies have shown that SA is reduced in individuals with schizophrenia [see, e.g., (13,43,44)]. This may account for the feeling of detachment over self-generated actions and sensations characterizing peculiar symptoms of this pathological condition, such as hallucinations and delusions of control. The question addressed in this paper is to what extent these findings can be replicated and whether they provide a sufficient mechanistic explanation of auditory hallucinations.

Cancellation model frameworks suggest a direct link between hallucinations and self-monitoring impairment. Feinberg (15,16) proposed that positive symptoms could result from impaired corollary discharge and forward model implementation, whereby altered corollary discharge may prevent distinguishing self-generated from external stimuli, thereby resulting in hallucinations. Frith (17,45) further elaborated this hypothesis by proposing that auditory hallucinations and delusions of control may be due to deficits in self-monitoring processes and a lack of awareness of intentions. In support of the hypothesis of deficient corollary discharge as a causal mechanism for hallucinations, Ford *et al.* (46) found that prespeech neural synchrony, a possible index of speech-related efference copy signaling, was inversely correlated with the severity of hallucinations: the lower the prespeech synchrony, the more severe the hallucinatory symptomatology (46).

Alternative hypotheses have been proposed in the domain of the predictive coding/Bayesian models framework. For Leptourgos and Corlett (36), strong high-order priors make the neural systems of patients with schizophrenia more vulnerable to positive symptoms; thus, delusions and hallucinations would manifest as consequences of a compensatory response to low-level perceptual aberrancies such as those arising from impaired SA (36).

Within the same framework, Yon *et al.* (37,38) have suggested that patients with schizophrenia may not be able to efficiently integrate prior knowledge with perceptual estimates, which may lead to the creation of unreliable representations of actions-consequences links, leaving them at the mercy of a perceptually noisy environment leading to uncertainty. In this context, unusual beliefs may be created to respond to such uncertainty and find ad hoc explanations for their actions and causes (37,38).

Finally, Tarasi *et al.* (47) have proposed that perceptual inference of patients with schizophrenia may be mostly driven by top-down priors (potentially due to overly precise priors or imprecise prediction errors) rather than by a balanced integration between priors and sensory evidence. Based on this approach, one may hypothesize that the SA deficiency in patients with schizophrenia may be the result of overly strong predictions for external sounds rather than weak sensorimotor predictions for self-generated sounds (47).

Clearly, besides their fine-grained differences, these models imply different mechanistic explanations of the relationship between SA and auditory hallucinations. According to earlier proposals by Feinberg and Frith, impaired SA would specifically reflect the causal mechanism of auditory hallucinations (15,16,45). If these theories held true, it would be reasonable to

Table 1. An Overview of the Most Accredited Interpretations of SA Phenomenon

Models	References	Interpretations to Explain the Phenomenon of SA
Attention Hypothesis	Horváth *et al.* (21), Okamoto *et al.* (22), Saupe *et al.* (23), Schröger *et al.* (24)	During motor planning and execution, our attention may be directed toward predictive aspects of the action generation rather than the produced sensory stimuli. Consequently, self-generated stimuli are perceived as less intense than externally generated stimuli to which attention is completely focused during perception. Accordingly, SA may result from a difference in attention allocation between self- and externally produced sensory stimuli.
Cancellation Models	Blakemore *et al.* (2), Blakemore *et al.* (3), Wolpert *et al.* (25), Helmholtz (26), Von Holst *et al.* (27), Sperry (28), Blakemore *et al.* (29), Shergill *et al.* (30)	When a voluntary movement is produced, an efference copy of the motor command is used through an internal forward model to produce corollary discharges, carrying predictions about the sensory consequences of the movement. These predictions are then compared with the actual sensory effects of the actions, and in the case of matching, they are used to attenuate the perception of sensory feedback itself. In this theoretical context, the motor system has a specific and direct role in determining SA: a "forward model" within the motor system effectively dampens activity in anticipated sensory units, enabling agents to disregard predictable sensations. This, in turn, ensures that they maintain heightened sensitivity to unforeseen outcomes, which is a crucial factor for learning and strategizing new actions. This hypothesis has been supported by several neuroimaging studies showing reduced brain activity in sensory brain regions [see (29,30)].
Pre-activation Theory	Roussel *et al.* (31), Waszak *et al.* (32)	Our brain creates representations of motor programs accompanied by their most plausible sensory consequences. In detail, while a motor program is planned and executed, the representation of the linked sensory information is also triggered, pre-activating and preparing the brain for a specific percept (i.e., increased activity in the sensory areas that represent expected action outcome). Consequently, if the actual sensory consequences match the predicted representation, the self-generated sensation will have less perceptual impact in terms of brain activations.
Predictive Coding Theories and Bayesian Accounts	Press *et al.* (19), Adams *et al.* (33), Sterzer *et al.* (34), Corlett *et al.* (35), Leptourgos *et al.* (36), Yon *et al.* (37), Yon *et al.* (38)	Our brain constantly tries to infer the cause of incoming sensory information by balancing prior beliefs about the cause of changes in perceptions and the actual sensory evidence. 1) According to Yon and Press (37,38), prior expectations are incorporated into sensory estimates by varying the weights on sensory channels and assigning "higher importance" to expected rather than unexpected sensory events (i.e., "sharpening models") [see (37,38)]. Accordingly, brain activity for incoming expected inputs should be suppressed, as postulated by the cancellation models, but only in "(neural) units tuned away from expected inputs, rather than in units tuned toward these inputs" [see (37)]. This pattern should be reversed in voxels tuned toward the expected stimulus [see (37,38)]. 2) Leptourgos and Corlett (36) proposed 2 interconnected hierarchies—an egocentric and an allocentric system—working in parallel and interacting at the sensory level. The egocentric system is based on the copy of the motor command, transformed into a sensory outcome prediction through a forward model, and transmitted to sensory areas, where it suppresses self-generated (predictable) inputs. On the other hand, the allocentric system encompasses generative causal models of the world, including the self as a potential cause. Allocentric predictions, akin to motor predictions, account for and explain away predictable inputs. Unlike the egocentric system, these inputs are not necessarily self-generated. Additionally, higher-level priors, such as intentionality or a self-attribution bias, can modulate allocentric predictions [see (36)].

SA, sensory attenuation.

expect hallucinating patients to show a more severe auditory SA deficiency.

On the other hand, more recent theories in the predictive coding framework seem to converge in suggesting that the altered SA would represent a sign of vulnerability for psychotic symptoms, such as hallucinations, rather than an explanatory mechanism (19,36–38,47). Thus, regardless of the specific mechanism responsible for SA, dysfunctional SA should predispose individuals to the onset of psychotic symptoms and not be a sufficient causal mechanism by itself. From this perspective, hallucinations should not stem directly from the impairment of SA-related mechanisms.

Aim of the Study

To address these issues, we performed 3 meta-analyses that tested the level of available evidence in the literature discussed above. In a first meta-analysis, we assessed whether patients with schizophrenia actually do show significant auditory SA, namely a reduced N1 amplitude in talking compared with listening conditions. The presence of SA would indicate at least a partial maintenance of predictive processes (e.g., corollary discharge mechanisms).

In a second meta-analysis, we considered the potential role of aspects scarcely explored in the literature that may affect SA in schizophrenia: the severity of auditory hallucinations and the possible effect of antipsychotic medication on N1 suppression.

In a third meta-analysis, we compared the N1 attenuation in patients with schizophrenia to that of healthy control participants; reduced SA may suggest altered predictive processes in schizophrenia. We also investigated whether the SA reduction is influenced by illness duration, expecting that illness progression and chronicity may influence SA.

Finally, we also assessed whether SA dysfunction is observed exclusively in patients who hallucinate or also in patients without hallucinations or in at-risk subjects; in the latter case, one could entertain the hypothesis that altered SA is just one more sign of a dysfunctional auditory sensory system, which is a risk factor for the occurrence of psychosis that could also be present in at-risk subjects rather than being a causal mechanism of hallucinations.

METHODS AND MATERIALS

We interrogated the PubMed database in September 2022. The flowchart and the description of this screening process are presented in the Supplement.

The final dataset included 15 papers and a total of 1394 participants, 784 patients with schizophrenia and nonclinical subjects within the schizophrenia spectrum (mean age 30.97 ± 8.46 years) and 610 healthy control participants (mean age 31.48 ± 13.27 years). See Tables 2 and 3 for a detailed description of the included studies.

All the studies assessed SA using electrophysiological measures by measuring the attenuation of N1 amplitude[1] elicited by self- versus externally generated sounds. We specifically focused on N1 data because the P2 component has not been reported in most of the studies measuring SA in patients with schizophrenia (48,49). In most cases, N1 amplitude was assessed in 2 conditions, an experimental condition in which participants produced auditory outcomes (talking) and a baseline condition characterized by the appearance of the same auditory stimuli but not directly controlled by participants (listening).

We extracted the values of N1 amplitude for self-generated sounds ($N1_{talking}$) and N1 for externally generated sounds ($N1_{listening}$) (Table S1)[2]. We calculated a variable called "$SA_{overall}$" by subtracting the N1 amplitude for self-generated sounds from the N1 amplitude for externally generated sounds ($SA_{overall} = N1_{listening} - N1_{talking}$). SA is characterized by a significantly higher (i.e., more negative) N1 amplitude for externally triggered sounds than for self-generated ones.

The SA overall standard deviation was calculated, as suggested by the Cochrane Handbook for systematic reviews (50), as follows:

$$SD_{SAoverall} = \left(SD_{N1listening}\right)^2 + \left(SD_{N1talking}\right)^2 - \sqrt{2 * corr * SD_{N1listening} * SD_{N1talking}} \quad (1)$$

First Meta-Analysis: Is SA Detectable in Patients With Schizophrenia?

In the first meta-analysis, we tested the hypothesis that SA might be recorded to some extent in patients with schizophrenia. Based on such a hypothesis, the attenuation of N1 is expected to be significantly different from 0 and, in particular, to be a negative value, according to a feature of the SA phenomenon (1,2): the more negative the value, the greater the difference between N1 for externally generated and self-generated sounds and the stronger the effect of suppression on N1 for self-generated sounds.

We included the studies that tested at least 1 group of individuals on the schizophrenia spectrum regardless of the presence of a healthy control group. Some of these studies contributed more than 1 value of N1 amplitude from the same patient sample, violating the independent assumption of independence of fixed- and random-effects meta-analyses (51,52). Thus, we performed a multilevel analysis (for further details, see the Supplement).

Second Meta-Analysis: Is SA Associated With Symptom Severity and Medication Treatment?

We added measures of positive symptom severity and medication dosage as moderators in the previous meta-analysis. The severity of symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) (53) and the Scale for the Assessment of Positive Symptoms (54). Scale for the Assessment of Positive Symptoms scores were converted to equivalent scores of the PANSS positive scale based on the method proposed by van Erp *et al.* (55). When considering the medication treatment effect, information about the dosage of chlorpromazine equivalents was used (https://cpnp.org/guideline/essentials/antipsychotic-dose-equivalents). We considered 9 studies for the first moderator (43,44,48,56–62) and 6 studies for the second moderator (43,44,46,48,56–58).

Third Meta-Analysis: Is SA Reduced in Patients With Schizophrenia?

In a third meta-analysis, we tested the hypothesis that the SA phenomenon is significantly reduced in patients with schizophrenia compared with healthy control participants. Based on this hypothesis, SA is expected to be significantly different in the 2 groups; in particular, SA should assume a more negative value in control participants than in patients (1,2). The more negative the value, the greater the difference between N1 for externally generated and self-generated sounds and the stronger the effect of suppression on N1 for self-generated sounds.

In this meta-analysis, we included studies that compared N1 attenuation in at least 1 group of individuals on the schizophrenia spectrum and at least 1 control group. However, some of these studies 1) contributed more than 1 value of N1 amplitude from the same patient's sample, and/or 2) compared more than 1 patient group with the same healthy control group. For this reason, we performed a multilevel analysis (see the Supplement for further details).

RESULTS

Before running each meta-analysis, we assessed between-study heterogeneity to identify possible influential cases and potential publication bias (see the Supplement).

First Meta-Analysis: Is SA Detectable in Patients With Schizophrenia?

The multilevel meta-analysis results indicated the presence of significant SA for self-generated sounds in patients with schizophrenia (overall SA: −1.04; 95% CI: −1.72 to −0.36, standard error = 0.33, p = .0045) (see the forest plot in Figure 1).

[1]Most of the studies applied a 2-channel reference correction (13,44–48,56–61,67–69); 1 study applied the average reference correction (43), and 1 study did not report details about the correction of raw data (58).

[2]Some of the studies included in the meta-analysis did not provide standard deviations of the N1 amplitude (43,44,48,50,56,59). To deal with this problem, we imputed missing standard deviations using one of the imputation methods proposed by Furukawa *et al.* (74). The authors suggested imputing an SD_{pooled}, which is the result of the summation of the SDs reported by the other studies included in the meta-analysis, divided by the sample size: $SD_{pooled} = \sqrt{\frac{\sum (n_i - 1)SD_i^2}{\sum (n_i - 1)}}$

Table 2. Details of the Studies Included in the Meta-Analyses

		Control Group		Patient Group						
Study	PMID	*N*(F)	Age, Years, Mean (±SD)	*N* (F)	Diagnosis	Age, Years, Mean (±SD)	PANSS Positive Symptoms, Mean (±SD)[a]	Med[b]	Dosage of Chlorpromazine Equivalents, mg/day, Mean (±SD)	EEG Sites
Bose *et al.* (62), 2019	30076111	–	–	13 (4)	SCZ+AH	33.3 (±7.2)	20.99[a,c]	N	–	Fz, Fcz
Bühler *et al.* (43), 2016	27209172	28 (14)	37.8 (±14.4)	14 (6)	SCZ/SZA+AH	42.1 (±10.1)	16.3 (±4.7)	Y	537.8 (±547.4)	Fz
				14 (5)	SCZ/SZA−AH	41.1 (±10.7)	15.3 (±3.6)	Y	504.5 (±420)	Fz
Ford *et al.* (13), 2001	11600107	7 (0)	35.9[c]	7 (0)	SCZ	34.1[c]	–	Y	–	Cz
Ford *et al.* (68), 2007	17565658	26 (7)	42.2 (±10.6)	27 (4)	SCZ/SZA	43 (±10.4)	–	Y	665.5[c]	Fz, Fcz, Cz, CPz, Pz
Ford *et al.* (46), 2007	17329471	25 (6)	42.1 (±10.8)	24 (4)	SCZ/SZA	42.4 (±10.7)	–	Y	–	–
Ford *et al.* (56), 2013	23155183	43 (21)	36.3 (±12.3)	30 (11)	SCZ	34.5 (±14.6)	19 (±6.4)	Y	494.25[c]	FCz
				19 (12)	SZA	36.6 (±13.6)	20.3 (±4.2)	Y	406.34[c]	FCz
Ford *et al.* (48), 2021	33621618	92 (19)	37.4 (±13.9)	96 (18)	SCZ	36.3 (±13.4)	12.8[a,c]	Y	–	Cz
Kort, *et al.* (58), 2017	27647218	33 (8)	34.2 (±8.9)	34 (8)	SCZ	34.7 (±9.8)	16.8 (±6.9)	Y	548 (±532.9)	Fz, FCz, Cz
Heinks-Maldonado *et al.* (57), 2007	17339517	17 (0)	36.1[c]	10 (0)	SCZ+AH	38.9[c]	18.8[a,c]	Y	–	Fcz—LH
				10 (0)	SCZ+AH	42.8[c]	13.27[a,c]	Y	–	Fcz—LH
Mathalon *et al.* (59), 2019	30249315	103 (42)	22.6 (±6.3)	84 (23)	ESCZ	21.9 (±4.1)	12.32[a,c]	Y	–	Cz
				71 (30)	HRP	19.4 (±4.7)	–	Y	–	Cz
Nawani *et al.* (61), 2014	24507573	–	–	5 (3)	SCZ+AH	33.2 (±19.3)	–	Y	483.3 (±189.5)	Cz
Oestrich *et al.* (69), 2015	26027781	37 (25)	20.6 (±3.4)	37 (22)	HSCT	23.2 (±5.7)	–	N	–	Cz
Perez *et al.* (67), 2012	21993915	75 (48)	30.4 (±10.6)	75 (20)	SCZ	28 (±11.6)	–	Y	–	Cz
		36 (15)	21.2 (±3.2)	35 (16)	HRSCZ	19.5 (±3.7)	–	N	–	Cz
				39 (9)	ESCZ	21.4 (±4)	–	Y	–	Cz
Roach *et al.* (44), 2019	30599145	29 (14)	22.5 (±5.9)	23 (7)	SCZ	23.4 (±4.3)	12.22[a,c]	Y	350.1 (±356.1)	Cz
				26 (6)	SCZ	21 (±3.9)		Y		Cz
Whitford *et al.* (60), 2018	29194516	59 (26)	21.4 (±5.9)	51 (19)	ESCZ	21.2 (±3.5)	12.25[a,c]	Y	–	Cz
				40 (15)	HRP	20.3 (±4)	–	Y	–	Cz

The dependent variable (measured in μV) for every included study was the N1 component in response to own voice sound.

AH, auditory hallucinations (+ indicates with; − indicates without); ESCZ, early stages of schizophrenia illness; F, female; HRP, individuals clinically at risk for developing psychosis; HRSCZ, individuals clinically at high risk for developing schizophrenia; HSCT, healthy participants with high schizotypy traits; Med, medication; PANSS, Positive and Negative Syndrome Scale; SCZ, individuals with schizophrenia; SZA, participants with schizoaffective disorder.

[a]Indicates scores converted from Scale for the Assessment of Positive Symptoms to equivalent scores of PANSS positive scale based on the method proposed by van Erp *et al*. (55).

[b]Medication state: Y indicates medicated, N indicates not medicated.

[c]SD not provided.

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Table 3. Summary of the Studies Included in the Meta-Analyses

Study	Sample	Inclusion and Exclusion Criteria	Experimental Task	Main Results	Association With Symptoms
Bose *et al.* (62), 2019	13 SCZ+AH	Inclusion criteria: diagnosis of schizophrenia (DSM-IV-TR) Exclusion criteria: not specified	Talk-Listen task: Talking: subjects speak and listen to their speech online. Listening: subjects passively listen to their prerecorded speech.	SCZ: similar N1 amplitudes recorded in response to hearing own speech during talking and listening conditions.	Not explored
Bühler *et al.* (43), 2016	14 SCZ/SZA+AH 14 SCZ/SZA−AH 28 CTR	Inclusion criteria: diagnosis of schizophrenia or schizoaffective psychosis (ICD-10) Exclusion criteria: not specified	Talk-Listen task: Talking: subjects read a word and listen to their voice. Listening: subjects listen to their prerecorded voice reading a word.	CTR: N1 amplitude recorded in response to hearing own words is significantly smaller during the talking condition than the listening condition. SCZ: the difference between N1 amplitudes recorded during talking and listening conditions is significantly smaller than in the CTR group for both +AH and −AH groups.	No significant correlation between the total score of the PANSS and the N1 suppression in SCZ+AH and SCZ−AH.
Ford *et al.* (13), 2001	7 SCZ 7 CTR	Inclusion criteria: diagnosis of schizophrenia (DSM-IV) Exclusion criteria: not specified	Talk-Listen task: Talking: subjects utter and listen to their produced vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during talking than the listening condition. SCZ: the difference between N1 amplitudes recorded during talking and listening conditions is significantly smaller than in the CTR group.	Not explored
Ford *et al.* (68), 2007	27 SCZ (12 undifferentiated, 9 paranoid, 4 SZA, 2 residual) 26 CTR	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) Exclusion criteria: alcohol or drug abuse within 30 days before the study. Head injury, neurological disorders, or other medical illnesses compromising the central nervous system.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	No significant correlation between N1 suppression and the BPRS items.
Ford *et al.* (46), 2007	24 SCZ (10 undifferentiated, 9 paranoid, 3 SZA, 2 residual) 25 CTR	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) Exclusion criteria: alcohol or drug abuse within 30 days before the study. Head injury, neurological disorders, or other medical illnesses compromising the central nervous system.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to own vocalizations is significantly smaller during the talking condition than during the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	Not explored.

Table 3. Continued

Study	Sample	Inclusion and Exclusion Criteria	Experimental Task	Main Results	Association With Symptoms
Ford *et al.* (56), 2013	30 SCZ 19 SZA 43 CTR	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) Exclusion criteria: presence of medical conditions that impact brain function. Head trauma with loss of consciousness for more than 10 minutes. Current substance use ascertained by urine drug screens on the day of testing. Drug abuse in the preceding 3 months or dependence within 6 months.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to the hearing of own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions. SZA: the difference between N1 amplitudes recorded during talking and listening conditions is significantly smaller than in the CTR group.	No significant correlations between N1 suppression and scores of the PANSS, YMRS, and MADRS in both groups of patients.
Ford *et al.* (48), 2021	96 SCZ 92 CTR	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) Exclusion criteria: estimated IQ $<$ 70. A history of significant medical or neurological illness. A history of head injury resulting in loss of consciousness.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: the difference between N1 amplitudes recorded during talking and listening conditions is significantly smaller than in the CTR group.	No significant correlation between the total scores of the SAPS and the N1 suppression in both tasks.
			Sing-Listen task: Singing: subjects sing and listen to their singing. Listening: subjects listen to their prerecorded singing.	CTR: similar N1 amplitudes recorded in response to hearing own vocalizations during singing and listening conditions. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during singing and listening conditions.	
Heinks-Maldonado *et al.* (57), 2007	10 SCZ+AH 10 SCZ−AH 17 CTR	Inclusion criteria: diagnosis of schizophrenia (DSM-IV) Exclusion criteria: hearing loss. Significant head injury (loss of consciousness over 30 minutes or resulting in neurological sequelae). Neurological or other medical illnesses compromising the central nervous system. DSM-IV alcohol or drug abuse within 30 days before the study.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ−AH: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions. SCZ+AH: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	The global score of the SAPS for hallucinations was significantly correlated with the amount of N1 suppression in the left hemisphere: the more severe the hallucinations, the more positive (abnormal) the suppression n value.

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Table 3. Continued

Study	Sample	Inclusion and Exclusion Criteria	Experimental Task	Main Results	Association With Symptoms
Kort *et al.* (58), 2017	34 SCZ 33 CTR	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) Exclusion criteria: alcohol or drug abuse within 30 days of study entry or dependence within the past year. Significant head injury. Neurological disorders. Other medical illnesses compromising the central nervous system.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	Not explored.
Mathalon *et al.* (59), 2019	84 ESCZ 71 HRP 103 CTR	Inclusion criteria for ESCZ: diagnosis of schizophrenia or schizoaffective disorder within 5 years (DSM-IV). Inclusion criteria for HRP: attenuated psychotic symptoms, brief intermittent psychotic states, or genetic risk with deterioration in social or occupational functioning (SIPS). Exclusion criteria: estimated IQ <70. A history of significant medical or neurological illness. A history of head injury resulting in loss of consciousness.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions. HRP: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	In the HRP group, unusual thought content was correlated with suppression of N1 during talk compared with listen, such that subjects with more unusual thought content showed less N1 suppression. This was not true for the other symptoms. No significant correlations existed between the N1 suppression score and the global score of the SAPS in the ESCZ group.
Nawani *et al.* (61), 2014	5 SCZ+AH	Inclusion criteria: persistence of daily AH without remission (AHRS). Diagnosis of schizophrenia (DSM-IV-TR). Exclusion criteria: any comorbid substance dependence, medical, or neurological disease. Any hearing impairment.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	Not explored.
Oestreich *et al.* (69), 2015	37 HSCT 37 LSCT	Inclusion criteria for HSCT: scoring in the upper quartile of the group on the SPQ Exclusion criteria: not specified	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	LSCT: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. HSCT: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	Significant negative correlation between the total SPQ score and N1 suppression, such that higher levels of schizotypy traits are associated with smaller N1 suppression effects.

Table 3. Continued

Study	Sample	Inclusion and Exclusion Criteria	Experimental Task	Main Results	Association With Symptoms
Perez *et al.* (67), 2012	75 SCZ 75 CTR 39 ESCZ 35 HRP 36 CTR	Inclusion criteria for ESCZ: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV). Within 2.5 years of initial hospitalization for psychosis or initiation of antipsychotic medication. Inclusion criteria for HRP: attenuated psychotic symptoms, brief intermittent psychotic states, or genetic risk with deterioration in social or occupational functioning (SIPS). Exclusion criteria: a history of substance dependence or abuse within the past year. A history of a significant medical or neurological illness. A history of head injury resulting in loss of consciousness.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions. CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. ESCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions. HRP: N1 amplitude recorded in response to hearing own vocalizations is smaller (even if not statistically) during the talking condition compared with the listening condition.	No significant correlation between N1 suppression and subscales of the PANSS.
Roach *et al.* (44), 2019	49 SCZ 29 CTR	Inclusion criteria for SCZ: diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder (DSM-IV). Within 5 years of initial hospitalization for psychosis or initiation of antipsychotic medication. Exclusion criteria: estimated IQ <70. A history of significant neurological illness. A history of substance abuse in the past year.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. SCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions.	No significant correlations were found between N1 suppression and the SAPS.
Whitford, *et al.* (60), 2018	51 ESCZ (DSM-IV) 40 HRP (SIPS) 59 CTR	Inclusion criteria for ESCZ: diagnosis of schizophrenia (DSM-IV). Within 2.5 years of their first hospitalization for psychosis and/or their first exposure to antipsychotic medication. Exclusion criteria: a history of head injury resulting in loss of consciousness. A history of significant neurological illness. A history of alcohol or substance abuse in the past year.	Talk-Listen task: Talking: subjects utter and listen to their vocalizations. Listening: subjects listen to their prerecorded vocalizations.	CTR: N1 amplitude recorded in response to hearing own vocalizations is significantly smaller during the talking condition than the listening condition. ESCZ: similar N1 amplitudes recorded in response to hearing own vocalizations during talking and listening conditions. HRP: the difference between N1 amplitudes recorded during talking and listening conditions is significantly smaller than in the CTR group.	Not explored.

AH, auditory hallucinations (+ indicates with; − indicates without); BPRS, Brief Psychiatric Rating Scale; CTR, healthy control; ESCZ, individuals at early stages of schizophrenia illness; HRP, individuals clinically at risk for developing psychosis; HSCT, individuals with high schizotypy traits; LSCT, individuals with low schizotypy traits; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms; SCZ, individuals with schizophrenia; SIPS, Structured Interview for Prodromal Syndrome; SPQ, Schizotypal Personality Questionnaire; SZA, participants with schizoaffective disorder; YMRS, Young Mania Rating Scale.

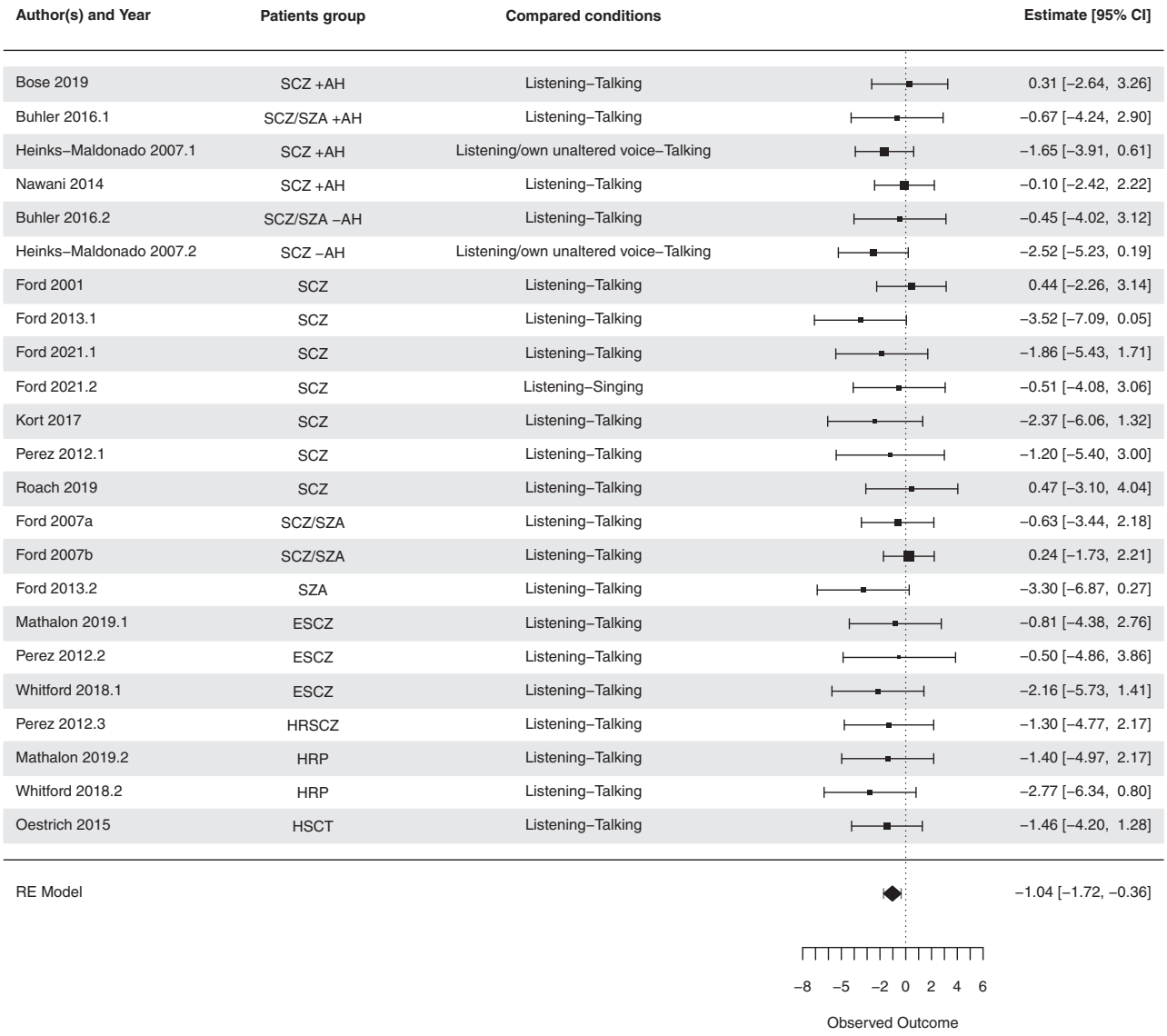

Figure 1. First meta-analysis: sensory attenuation in individuals on the schizophrenia spectrum. The black diamond indicates the summary estimate based on the model; the center of the diamond corresponds to the estimate, and the left/right edges indicate the confidence interval limits. The figure also shows the estimated values of sensory attenuation overall measure (observed outcome) for each study (black squares), calculated as the N1 amplitude difference between self- and externally generated sounds and the 95% CIs; the larger the square, the lower the variability of the data included in that study. AH, auditory hallucinations (+ indicates with; − indicates without), ESCZ, early stages of schizophrenia illness; HRP, individuals clinically at high risk for developing psychosis; HRSCZ, individuals clinically at high risk for developing schizophrenia; HSCT, healthy participants with high schizotypy traits; SCZ, participants with schizophrenia; SZA, participants with schizoaffective disorder.

Second Meta-Analysis: Is SA Associated With Symptom Severity and Medication Treatment?

No significant effect was found when considering the severity of positive symptoms (beta PANSS scores = −0.017, $p = .89$, standard error = 0.13, 95% CI: −0.31 to 0.27, $F_{1,13} = 0.017$) (see Figure 2A) and chlorpromazine equivalent dosage (beta chlorpromazine dosage = 0.005, $p = .55$, standard error = 0.009, 95% CI: −0.02 to 0.03, $F_{1,5} = 0.39$) (see Figure 2B).

Third Meta-Analysis: Is SA Reduced in Patients With Schizophrenia?

The multilevel meta-analysis results indicated the existence of a significant difference in SA between healthy control participants and patients with schizophrenia (SA patients with schizophrenia: −1.19; 95% CI: −1.93 to −0.46, standard error = 0.35, $p = .0028$; SA healthy control participants: −2.95; 95% CI: −3.95 to −1.95, standard error = 0.46, $p < .0001$) (see the forest plot in Figure 3).

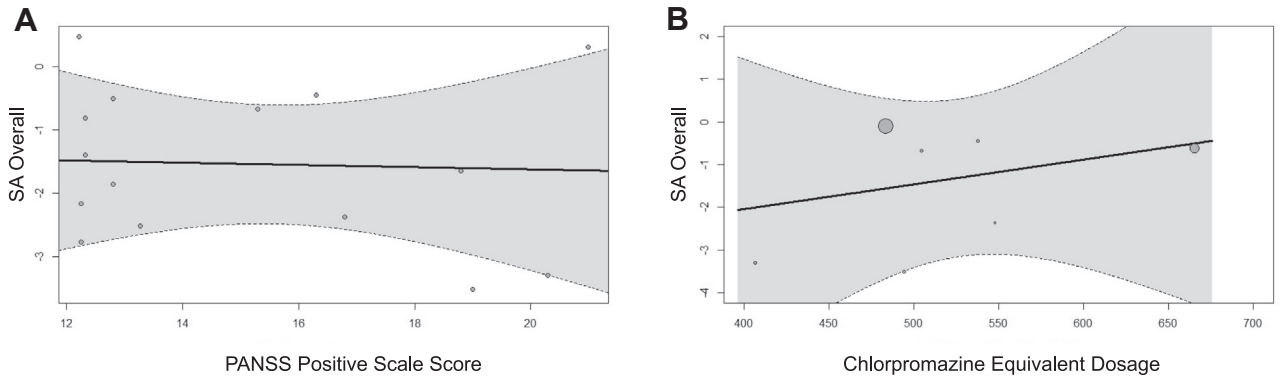

Figure 2. **(A)** Second meta-analysis: sensory attenuation (SA) in individuals with schizophrenia with the severity of the symptoms inserted as moderator [x-axis, Positive and Negative Syndrome Scale [PANSS] scores converted by the method of van Erp *et al.* (55); y-axis, N1 amplitude difference between self- and externally generated; the circle size reflects the weight of each considered study in the model, defined by the variability (73)]. **(B)** Second meta-analysis: SA in individuals with schizophrenia with medication treatment dosage inserted as moderator [x-axis, chlorpromazine equivalent dosage calculated according to https://cpnp.org/guideline/essentials/antipsychotic-dose-equivalents; y-axis, N1 amplitude difference between self- and externally generated; a circle in different sizes represents each study to reflect their weight in the model, defined by the variability (73)].

Summary of the Results

To sum up, our meta-analyses indicate that individuals who are on the schizophrenia spectrum show SA, and its magnitude is independent from the severity of positive symptomatology and medication. In fact, the N1 amplitude difference between talking and listening conditions was significantly lower than 0.

However, we also observed that the magnitude of the SA measured in the patients was significantly smaller than the same measure collected in healthy control participants. The qualitative exploration depicted in Figure 3 indicates that patients in the early stages of the illness (highlighted in green) show reduced SA that is similar to that of chronic patients (highlighted in gray). Moreover, patients without hallucinations (highlighted in blue), as well as nonclinical individuals who are on the schizophrenia spectrum (who did not have a history of full-blown psychotic symptoms, highlighted in yellow) show reduced SA similar to that seen in patients with hallucinations (highlighted in red).

In other words, the less prominent SA that we observed in people on the schizophrenia spectrum seems not to be influenced by the presence of hallucinations and the stage of the illness.

DISCUSSION

To our knowledge, this is the first quantitative review of the existing literature on auditory SA in individuals on the schizophrenia spectrum. In this section, we will discuss our results in detail while considering the relevant neurocognitive models of schizophrenia that address the peculiar symptoms of the syndrome within the conceptual framework of SA and predictive processes.

Auditory SA Is Also Present in Schizophrenia Spectrum Disorders

The first meta-analysis provides clear evidence that SA occurs, at least to some extent, in these patients as well. As much as SA may depend on predictive mechanisms (3), this evidence would suggest a partial preservation of such mechanisms. Of course, we are aware that this conclusion should be treated with caution. As mentioned in the Methods and Materials section, all the studies included in our meta-analysis assessed auditory SA by subtracting the N1 amplitude elicited by externally generated speech sounds from the N1 amplitude of self-generated speech sounds. Given this choice, one may wonder whether these observations could be generalized; reassuringly, similar results (a reduced N1 for self-generated sounds) have been reported in tasks where patients listened to tones rather than speech generated by their button pressing as opposed to tones generated by others (49,63).

As Hughes (64) suggested, the 2 conditions (self- and externally generated sounds) do not allow for isolating the effect of predictive processes because they also differ in other crucial aspects that could partially explain SA. In particular, the 2 conditions differ in terms of 1) temporal prediction, the possibility to predict the moment at which a sensory event will occur; 2) temporal control, the possibility to control the moment at which a sensory event will occur; and 3) prediction of the nature of the consequences of action, i.e., the possibility to predict, based on intended actions, the sensory event that will occur (64). However, even if somewhat confounded, it cannot be denied that the task difference that brings about the SA contains predictive processes implied by the active nature of the crucial task, which is voluntary speaking in the case reviewed here.

Thus, while acknowledging those potential limitations, we still propose that the consistent SA observed in patients with schizophrenia may represent a sign of partial preservation of predictive processes that are most likely at the root of the same phenomenon in healthy populations (64).

We conducted a regression analysis to further explore the relationship between SA and symptom severity. We found that patients' SA was not significantly correlated with PANSS scores (53). This finding challenges previous assumptions that auditory hallucinations may be caused by impaired SA (15–17)

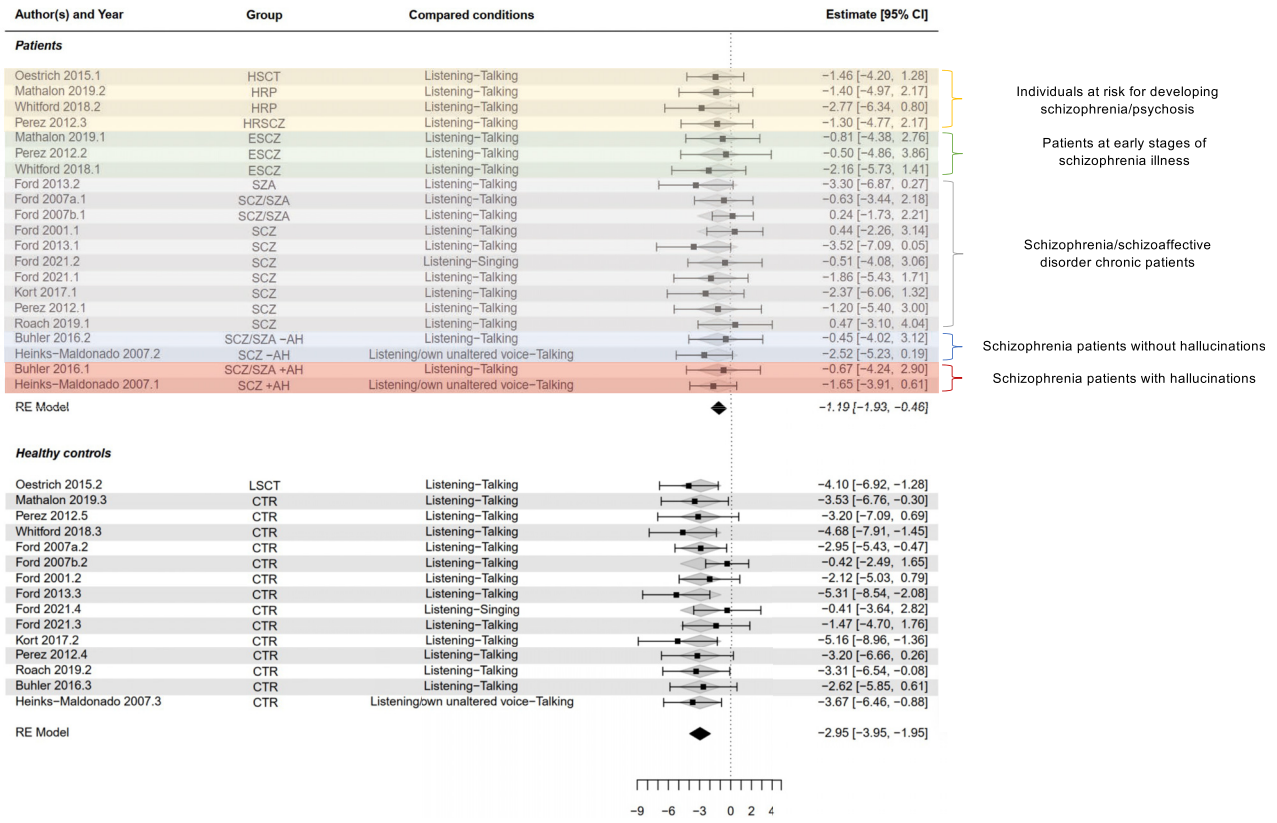

Figure 3. Third meta-analysis: sensory attenuation differences between individuals on the schizophrenia spectrum and healthy control participants. The number of patient studies differs from the first meta-analysis because we excluded studies that did not have at least 1 control group [e.g., (61,62)]. Moreover, there are more patient studies than control studies because some of the studies included in this meta-analysis compared more than 1 patient group with the same control group [e.g., (43,56,57,59,60,67)]. The black diamond indicates the summary estimate based on the model; the gray diamond is the summary estimate based on the model compared with each estimation; the center of the diamond corresponds to the estimate, and the left/right edges indicate the confidence interval limits. The figure also shows the estimated values of sensory attenuation overall measure (observed outcome) for each study (black squares), calculated as the N1 amplitude difference between self- and externally generated sounds and the 95% CI; the larger the square, the lower the variability of the data included in that study. AH, auditory hallucinations (+ indicates with; − indicates without); CTR, control participants; ESCZ, early stages of schizophrenia illness; HRP, individuals clinically at high risk for developing psychosis; HRSCZ, individuals clinically at high risk for developing schizophrenia; HSCT, healthy participants with high schizotypy traits; LSCT, healthy participants with low schizotypy traits; SCZ, participants with schizophrenia; SZA, participants with schizoaffective disorder.

and suggests that they may be triggered by maladaptive processes that are not directly or not entirely related to the SA reduction.

We also explored the impact of antipsychotic medication on SA magnitude. As far as the available literature and our analyses permit us to say, antipsychotic assumption does not have a sizable impact on the magnitude of SA in patients. Furthermore, subjects who are at risk or in a preclinical stage of the disorder also have reduced SA (as further discussed in the following paragraph). Taken together, these facts make it unlikely that a general effect of neuroleptic medication can be a sufficient cause of reduced SA, as previously suggested by Ford (65) and Heinks-Maldonado *et al.* (57).

It should be noted that these additional analyses were based on a few studies (9 for the analysis of symptom severity and 6 for the regression of medication dosage). Clearly, more studies are needed to settle these issues.

Moreover, the association between symptom severity and auditory SA is limited by the fact that patients may show different responsiveness to antipsychotics, from complete elimination to some reduction of symptoms. Given this, what the correlation really captures may represent the relationship between different levels of residual symptoms and SA (66).

Reduced SA in Patients With Schizophrenia Compared With Healthy Control Participants

When we compared the magnitude of the SA of patients and healthy control participants, we found that SA was significantly reduced in the patients. Even if we cannot directly investigate whether SA dysfunction in schizophrenia is due to impairments in corollary discharge, allocation of attention, pre-activation mechanisms, or a combination of them, we can suggest that impaired SA cannot be considered alone as the causal mechanism of auditory hallucinations and make some remarks.

SA seems not to be influenced by the stage of the illness; patients with early illness and chronic patients show similar

magnitudes of N1 attenuation values, indicating that dysfunctional SA is already present during earlier phases of the disease (59,60,67) and does not worsen with illness progression or chronicity.

In addition, the SA reduction is similar across studies that have included patients with and without auditory hallucinations. This implies that SA dysfunctions cannot be the unique explanation for the occurrence of positive symptoms such as auditory hallucinations. Multiple studies have reported this lack of correlation, strengthening the idea that SA deficits are not a sufficient cause for the manifestation of positive symptoms in schizophrenia (43,44,48,56,59,67–69). Thus, reduced SA could be seen as a risk factor for developing hallucinations, and if so, it becomes less surprising that it could also be observed in nonhallucinating patients and nonclinical subjects on the schizophrenia spectrum.

This is coherent with the proposal by Ford *et al.* (70) defining SA deficiency as an elementary deficit that enhances the predisposition to psychosis rather than being the pathophysiological mechanism that gives rise to auditory hallucinations (70). The observation in our meta-analysis of similar SA reduction in individuals who do not exhibit full-blown psychotic symptoms, e.g., individuals with high schizotypy (69) or individuals at high clinical risk of psychosis (59,60,67), provides additional support for this idea.

We acknowledge that there are several hypotheses about the neurophysiological mechanism underlying SA alterations in schizophrenia and how SA should/could be integrated with more recent theories such as those on predictive coding and related Bayesian models. Unfortunately, the measure considered for our investigation does not allow any specific conclusion to be drawn about this.

Having said that, we believe that theories proposed in the context of predictive coding and Bayesian accounts could better explain it (19,36–38,47). In fact, they converge in suggesting that SA-related defective predictive mechanisms lay the basis for the development of hallucinations, which represent a compensation strategy for patients to overcome sensory uncertainties. Accordingly, reduced SA may represent an example of these impaired predictive processes, contributing to not reducing sensory noise.

Of course, to fully support a predictive coding/Bayesian account of empirical data, one would need a simultaneous measure of SA and some sort of prior beliefs held by the patients, something that is not in the literature yet. Accordingly, for the time being, all we can say is that the theories that have been proposed in the context of predictive coding and Bayesian accounts may represent valid progress in the field inasmuch as they will be able to model schizophrenia by considering that defective SA is present in the schizophrenia spectrum independent of the presence of hallucinations.

Conclusions

Our results, while supporting the idea that reduced SA is a trait of people on the schizophrenic spectrum, also foster the idea that altered SA is not a sufficient explanatory mechanism for auditory hallucinations. Because of its presence in the prodromic phases of the disorder, impaired SA may be a sign of a more general sensory processing dysfunction, i.e., a risk factor rather than the causal mechanism for psychosis.

It should be noted that all the studies included in this work investigated SA during overt speech production. This may not straightforwardly test Feinberg's and Frith's hypotheses, according to which auditory hallucinations would be caused by the deficient attenuation of inner thoughts. In principle, processes that dampen the perception of overt speech may not be the same as those operating over inner thoughts. This, of course, partially limits the strength of the conclusions that we can draw on that theory.

Finally, it also must be acknowledged that the current results offer an incomplete sampling of the phenomenology of schizophrenia and cannot provide straightforward support to the predictive coding account of psychosis either. Indeed, SA pertains to phenomena outside the domain of higher-level factors that can influence sensorimotor integration processes in a top-down manner, such as motor intentions, background beliefs, and contextual cues (71). The investigation of experimental indices other than SA may shed more light on the role of other processes putatively related to the ability to attribute causality in schizophrenia [see (72)].

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ARTICLE INFORMATION

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